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HYDROXY ALKYL AMINES**BACKGROUND OF THE INVENTION**

5 This application claims priority from U.S. Provisional Application Serial No. 60/343,772, filed December 28, 2001, U.S. Provisional Application Serial No. 60/332,639, filed November 19, 2001, and U.S. Provisional Application Serial No. 60/295,332, filed June 1, 2001.

Field of the Invention

10 The invention relates to hydroxy alkylamine derivates and to such compounds that are useful in the treatment of Alzheimer's disease and similar diseases. More specifically the invention is directed to such compounds that are capable of inhibiting beta-secretase, an enzyme that cleaves amyloid precursor protein to produce amyloid beta peptide (A-beta), a major component of the amyloid plaques found in the brains of Alzheimer's sufferers.

Description of the Related Art

20 Alzheimer's disease (AD) is a progressive degenerative disease of the brain primarily associated with aging. Clinical presentation of AD is characterized by loss of memory, cognition, reasoning, judgment, and orientation. As the disease progresses, motor, sensory, and linguistic abilities are also affected until there is global impairment of multiple cognitive functions. These cognitive losses occur gradually, but typically lead to severe impairment and eventual death in the range of four to twelve years.

30 Alzheimer's disease is characterized by two major pathologic observations in the brain: neurofibrillary tangles and beta amyloid (or neuritic) plaques, comprised predominantly of an aggregate of a peptide fragment know as A-beta.

Individuals with AD exhibit characteristic beta-amyloid deposits in the brain (beta amyloid plaques) and in cerebral blood vessels (beta amyloid angiopathy) as as neurofibrillary tangles. Neurofibrillary tangles occur not only in Alzheimer's disease but also in other dementia-inducing disorders. On autopsy, large numbers of these lesions are generally found in areas of the human brain important for memory and cognition.

Smaller numbers of these lesions in a more restricted anatomical distribution are found in the brains of most aged humans who do not have clinical AD. Amyloidogenic plaques and vascular amyloid angiopathy also characterize the brains of individuals with Trisomy 21 (Down's Syndrome), Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type (HCHWA-D), and other neurogenerative disorders. Beta-amyloid is a defining feature of AD, now believed to be a causative precursor or factor in the development of disease. Deposition of A-beta in areas of the brain responsible for cognitive activities is a major factor in the development of AD. Beta-amyloid plaques are predominantly composed of amyloid beta peptide (A-beta, also sometimes designated betaA4). A-beta peptide is derived by proteolysis of the amyloid precursor protein (APP) and is comprised of 39-42 amino acids. Several proteases called secretases are involved in the processing of APP.

Cleavage of APP at the N-terminus of the A-beta peptide by beta-secretase and at the C-terminus by one or more gamma-secretases constitutes the beta-amyloidogenic pathway, i.e. the pathway by which A-beta is formed. Cleavage of APP by alpha-secretase and the same or a different gamma-secretase produces alpha-sAPP, a secreted form of APP that does not result in beta-amyloid plaque formation. This alternate pathway precludes the formation of A-beta peptide. A description of the proteolytic processing fragments of APP is found, for example, in U.S. Patent Nos. 5,441,870; 5,721,130; and 5,942,400.

An aspartyl protease has been identified as the enzyme responsible for processing of APP at the beta-secretase cleavage site. The beta-secretase enzyme has been disclosed using varied nomenclature, including BACE, Asp, am Mamepsin.

5 See, for example, Sindha et.al., 1999, *Nature* 402:537-554 (p501) and published PCT application WO00/17369.

Several lines of evidence indicate that progressive cerebral deposition of beta-amyloid peptide (A-beta) plays a seminal role in the pathogenesis of AD and can precede
10 cognitive symptoms by years or decades. See, for example, Selkoe, 1991, *Neuron* 6:487. Release of A-beta from neuronal cells grown in culture and the presence of A-beta in cerebrospinal fluid (CSF) of both normal individuals and AD patients has been demonstrated. See, for example, Seubert et
15 al., 1992, *Nature* 359:325-327.

It has been proposed that A-beta peptide accumulates as a result of APP processing by beta-secretase, thus inhibition of this enzyme's activity is desirable for the treatment of AD. In vivo processing of APP at the beta-secretase cleavage site
20 is thought to be a rate-limiting step in A-beta production, and is thus a therapeutic target for the treatment of AD. See for example, Sabbagh, M., et al., 1997, *Alz. Dis. Rev.* 3, 1-19.

BACE1 knockout mice fail to produce A-beta, and present a normal phenotype. When crossed with transgenic mice that over
25 express APP, the progeny show reduced amounts of A-beta in brain extracts as compared with control animals (Luo et.al., 2001 *Nature Neuroscience* 4:231-232). This evidence further supports the proposal that inhibition of beta-secretase activity and reduction of A-beta in the brain provides a
30 therapeutic method for the treatment of AD and other beta amyloid disorders.

At present there are no effective treatments for halting, preventing, or reversing the progression of Alzheimer's disease. Therefore, there is an urgent need for pharmaceutical

agents capable of slowing the progression of Alzheimer's disease and/or preventing it in the first place.

Compounds that are effective inhibitors of beta-secretase, that inhibit beta-secretase-mediated cleavage of APP, that are
5 effective inhibitors of A-beta production, and/or are effective to reduce amyloid beta deposits or plaques, are needed for the treatment and prevention of disease characterized by amyloid beta deposits or plaques, such as AD.

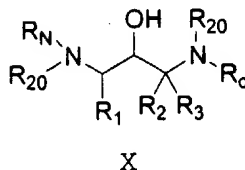
Various pharmaceutical agents have been proposed for the
10 treatment of Alzheimer's disease but without any real success.

Compounds that are effective inhibitors of beta-secretase activity, that inhibit beta-secretase-mediated cleavage of APP, or that are effective inhibitors of A-beta production or deposition are needed for the treatment and prevention of
15 disease characterized by beta-amyloid deposits or plaques, including AD.

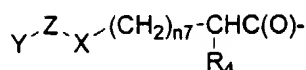
At present there are no effective treatments for halting, preventing, or reversing the progression of Alzheimer's disease. There is an urgent need for compounds capable of
20 slowing A-beta peptide production and/or deposition in the brain, which presents a therapeutic approach to treatment of Alzheimer's disease.

Summary of the Invention

In a broad aspect, the invention provides compounds of the formula X



and the pharmaceutically acceptable salts thereof, wherein R_N is:



wherein

- R_4 is selected from the group consisting of H; NH_2 ; $-\text{NH}-(\text{CH}_2)_{n6}$; R_{4-1} ; $-\text{NHR}_8$; $-\text{NR}_{50}\text{C}(\text{O})\text{R}_5$; C_1 - C_4 alkyl- $\text{NHC}(\text{O})\text{R}_5$; $-(\text{CH}_2)_{0-4}\text{R}_8$; $-\text{O}-\text{C}_1$ - C_4 alkanoyl; OH; C_6 - C_{10} aryloxy optionally substituted with 1, 2, or 3 groups that are independently halogen, C_1 - C_4 alkyl, $-\text{CO}_2\text{H}$, $-\text{C}(\text{O})-\text{C}_1$ - C_4 alkoxy, or C_1 - C_4 alkoxy; C_1 - C_6 alkoxy; aryl C_1 - C_4 alkoxy; $-\text{NR}_{50}\text{CO}_2\text{R}_{51}$; $-\text{C}_1$ - C_4 alkyl- $\text{NR}_{50}\text{CO}_2\text{R}_{51}$; $-\text{C}\equiv\text{N}$; $-\text{CF}_3$; $-\text{CF}_2-\text{CF}_3$; $-\text{C}\equiv\text{CH}$; $-\text{CH}_2-\text{CH}=\text{CH}_2$; $-(\text{CH}_2)_{1-4}-\text{R}_{4-1}$; $-(\text{CH}_2)_{1-4}-\text{NH}-\text{R}_{4-1}$; $-\text{O}-(\text{CH}_2)_{n6}-\text{R}_{4-1}$; $-\text{S}-(\text{CH}_2)_{n6}-\text{R}_{4-1}$; $-(\text{CH}_2)_{0-4}-\text{NHC}(\text{O})-(\text{CH}_2)_{0-6}-\text{R}_{52}$; $-(\text{CH}_2)_{0-4}-\text{R}_{53}-(\text{CH}_2)_{0-4}-\text{R}_{54}$;

wherein

- n_6 is 0, 1, 2, or 3;
 n_7 is 0, 1, 2, or 3;
 R_{4-1} is selected from the group consisting of $-\text{SO}_2-(\text{C}_1-\text{C}_8 \text{ alkyl})$, $-\text{SO}-(\text{C}_1-\text{C}_8 \text{ alkyl})$, $-\text{S}-(\text{C}_1-\text{C}_8 \text{ alkyl})$, $-\text{S}-\text{CO}-(\text{C}_1-\text{C}_6 \text{ alkyl})$, $-\text{SO}_2-\text{NR}_{4-2}\text{R}_{4-3}$; $-\text{CO}-\text{C}_1-\text{C}_2 \text{ alkyl}$; $-\text{CO}-\text{NR}_{4-3}\text{R}_{4-4}$;
 R_{4-2} and R_{4-3} are independently H, C_1 - C_3 alkyl, or C_3 - C_6 cycloalkyl;
 R_{4-4} is alkyl, arylalkyl, alkanoyl, or arylalkanoyl;
 R_{4-6} is-H or C_1 - C_6 alkyl;
 R_5 is selected from the group consisting of C_3 - C_7 cycloalkyl; C_1 - C_6 alkyl optionally substituted with

1, 2, or 3 groups that are independently halogen, -
NR₆R₇, C₁-C₄ alkoxy, C₅-C₆ heterocycloalkyl, C₅-C₆
heteroaryl, C₆-C₁₀ aryl, C₃-C₇ cycloalkyl C₁-C₄ alkyl,
-S-C₁-C₄ alkyl, -SO₂-C₁-C₄ alkyl, -CO₂H, -CONR₆R₇, -CO₂-
C₁-C₄ alkyl, C₆-C₁₀ aryloxy; heteroaryl optionally
substituted with 1, 2, or 3 groups that are
independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, C₁-C₄
haloalkyl, or OH; heterocycloalkyl optionally
substituted with 1, 2, or 3 groups that are
independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, or
C₂-C₄ alkanoyl; aryl optionally substituted with 1,
2, 3, or 4 groups that are independently halogen, OH,
C₁-C₄ alkyl, C₁-C₄ alkoxy, or C₁-C₄ haloalkyl; and -
NR₆R₇; wherein

R₆ and R₇ are independently selected from the group
consisting of H, C₁-C₆ alkyl, C₂-C₆ alkanoyl,
phenyl, -SO₂-C₁-C₄ alkyl, phenyl C₁-C₄ alkyl;
R₈ is selected from the group consisting of -SO₂-
heteroaryl, -SO₂-aryl, -SO₂-heterocycloalkyl, -SO₂-C₁-
C₁₀ alkyl, -C(O)NHR₉, heterocycloalkyl, -S-C₁-C₆
alkyl, -S-C₂-C₄ alkanoyl, wherein
R₉ is aryl C₁-C₄ alkyl, C₁-C₆ alkyl, or H;

R₅₀ is H or C₁-C₆ alkyl;

R₅₁ is selected from the group consisting of aryl C₁-C₄
alkyl; C₁-C₆ alkyl optionally substituted with 1, 2,
or 3 groups that are independently halogen, cyano,
heteroaryl, -NR₆R₇, -C(O)NR₆R₇, C₃-C₇ cycloalkyl, or
-C₁-C₄ alkoxy; heterocycloalkyl optionally
substituted with 1 or 2 groups that are independently
C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, C₂-C₄ alkanoyl,
aryl C₁-C₄ alkyl, and -SO₂ C₁-C₄ alkyl; alkenyl;
alkynyl; heteroaryl optionally substituted with 1, 2,
or 3 groups that are independently OH, C₁-C₄ alkyl,
C₁-C₄ alkoxy, halogen, NH₂, NH(C₁-C₆ alkyl) or N(C₁-C₆

hydroxyalkyl, alkanoyl, NO₂, CN, alkoxycarbonyl, or
aminocarbonyl;

X is selected from the group consisting of -C₁-C₆ alkylidenyl
optionally optionally substituted with 1, 2, or 3 methyl
5 groups; and -NR₄₋₆-; or

R₄ and R₄₋₆ combine to form -(CH₂)_{n10}-, wherein
n₁₀ is 1, 2, 3, or 4;

Z is selected from the group consisting of a bond; SO₂; SO; S;
and C(O);

10 Y is selected from the group consisting of H; C₁-C₄ haloalkyl;
C₅-C₆ heterocycloalkyl; C₆-C₁₀ aryl; OH; -N(Y₁)(Y₂); C₁-C₁₀
alkyl optionally substituted with 1 thru 3 substituents
which can be the same or different and are selected from
the group consisting of halogen, hydroxy, alkoxy,
15 thioalkoxy, and haloalkoxy; C₃-C₈ cycloalkyl optionally
substituted with 1, 2, or 3 groups independently selected
from C₁-C₃ alkyl, and halogen; alkoxy; aryl optionally
substituted with halogen, alkyl, alkoxy, CN or NO₂;
arylalkyl optionally substituted with halogen, alkyl,
20 alkoxy, CN or NO₂; wherein

Y₁ and Y₂ are the same or different and are H; C₁-C₁₀ alkyl
optionally substituted with 1, 2, or 3 substituents
selected from the group consisting of halogen, C₁-C₄
alkoxy, C₃-C₈ cycloalkyl, and OH; C₂-C₆ alkenyl; C₂-C₆
25 alkanoyl; phenyl; -SO₂-C₁-C₄ alkyl; phenyl C₁-C₄
alkyl; or C₃-C₈ cycloalkyl C₁-C₄ alkyl; or

Y₁, Y₂ and the nitrogen to which they are attached form a
ring selected from the group consisting of
piperazinyl, piperidinyl, morpholinyl, and
30 pyrrolidinyl, wherein each ring is optionally
substituted with 1, 2, 3, or 4 groups that are
independently C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkoxy
C₁-C₆ alkyl, or halogen;

R₂₀ at each occurrence is independently selected from the group consisting of hydrogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkoxy C₁-C₆ alkyl, hydroxy C₁-C₆ alkyl, halo C₁-C₆ alkyl, C₁-C₆ alkanoyl, each of which is unsubstituted or
5 substituted with 1, 2, 3, or 4 groups independently selected from halogen, alkyl, hydroxy, alkoxy, and NH₂, and -R₂₆-R₂₇, wherein

R₂₆ is selected from the group consisting of -C(O)-, -SO₂-, -CO₂-, -C(O)NH-, and -C(O)N(C₁-C₆ alkyl)-;

10 R₂₇ is selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, aryl C₁-C₆ alkyl, heterocycloalkyl, and heteroaryl, wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently C₁-C₄ alkyl, C₁-C₄
15 alkoxy, halogen, haloalkyl, hydroxyalkyl, -C(O)NH₂, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)(C₁-C₆ alkyl), -C(O)NH(C₁-C₆ alkyl), -C(O)N(C₁-C₆ alkyl)(C₁-C₆ alkyl);

R₁ is -(CH₂)₁₋₂-S(O)₀₋₂-(C₁-C₆ alkyl), or

C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 groups
20 independently selected from halogen, OH, =O, -SH, -C≡N, -CF₃, -C₁-C₃ alkoxy, amino, mono- or dialkylamino, -N(R)C(O)R'-, -OC(=O)-amino and -OC(=O)-mono- or dialkylamino, or

C₂-C₆ alkenyl or C₂-C₆ alkynyl, each of which is optionally
25 substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, and mono- or dialkylamino, or aryl, heteroaryl, heterocyclyl, -C₁-C₆ alkyl-aryl, -C₁-C₆ alkyl-heteroaryl, or -C₁-C₆ alkyl-heterocyclyl, where
30 the ring portions of each are optionally substituted with 1, 2, 3, or 4 groups independently selected from halogen, -OH, -SH, -C≡N, -NR₁₀₅R'₁₀₅, -CO₂R, -N(R)COR', or -N(R)SO₂R', -C(=O)-(C₁-C₄) alkyl, -SO₂-amino, -SO₂-

mono or dialkylamino, -C(=O)-amino, -C(=O)-mono or dialkylamino, -SO₂-(C₁-C₄) alkyl, or

-C₁-C₆ alkoxy optionally substituted with 1, 2, or 3 groups which are independently a halogen, or

5 C₃-C₇ cycloalkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, -C₁-C₆ alkyl and mono- or dialkylamino, or

10 C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, -C₁-C₃ alkoxy, amino, mono- or dialkylamino and -C₁-C₃ alkyl, or

15 C₂-C₁₀ alkenyl or C₂-C₁₀ alkynyl each of which is optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, C₁-C₆ alkyl and mono- or dialkylamino; and

the heterocyclyl group is optionally further substituted with oxo;

20 R and R' independently are hydrogen or C₁-C₁₀ alkyl;

R₂ is selected from the group consisting of H; C₁-C₆ alkyl, optionally substituted with 1, 2, or 3 substituents that are independently selected from the group consisting of C₁-C₃ alkyl, halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, and -NR_{1-a}R_{1-b}; wherein

25 R_{1-a} and R_{1-b} are -H or C₁-C₆ alkyl;

-(CH₂)₀₋₄-aryl; -(CH₂)₀₋₄-heteroaryl; C₂-C₆ alkenyl; C₂-C₆ alkynyl; -CONR_{N-2}R_{N-3}; -SO₂NR_{N-2}R_{N-3}; -CO₂H; and -CO₂-(C₁-C₄ alkyl);

30 R₃ is selected from the group consisting of H; C₁-C₆ alkyl, optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of C₁-C₃ alkyl, halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, and -

$\text{NR}_{1-a}\text{R}_{1-b}$; $-(\text{CH}_2)_{0-4}\text{-aryl}$; $-(\text{CH}_2)_{0-4}\text{-heteroaryl}$; $\text{C}_2\text{-C}_6$ alkenyl;
 $\text{C}_2\text{-C}_6$ alkynyl; $-\text{CO-NR}_{N-2}\text{R}_{N-3}$; $-\text{SO}_2\text{-NR}_{N-2}\text{R}_{N-3}$; $-\text{CO}_2\text{H}$; and $-\text{CO-}$
 $\text{O-(C}_1\text{-C}_4\text{ alkyl)}$;

or

- 5 R_2 , R_3 and the carbon to which they are attached form a carbocycle of three thru seven carbon atoms, wherein one carbon atom is optionally replaced by a group selected from $-\text{O-}$, $-\text{S-}$, $-\text{SO}_2\text{-}$, or $-\text{NR}_{N-2}\text{-}$;

R_c is selected from the group consisting of $\text{C}_1\text{-C}_{10}$ alkyl

- 10 optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of R_{205} , $-\text{OC=ONR}_{235}\text{R}_{240}$, $-\text{S(=O)}_{0-2}(\text{C}_1\text{-C}_6\text{ alkyl})$, $-\text{SH}$, $-\text{NR}_{235}\text{C=ONR}_{235}\text{R}_{240}$, $-\text{C=ONR}_{235}\text{R}_{240}$, and $-\text{S(=O)}_2\text{NR}_{235}\text{R}_{240}$; $-(\text{CH}_2)_{0-3}\text{-(C}_3\text{-C}_8\text{)}$ cycloalkyl wherein the cycloalkyl is optionally
- 15 substituted with 1, 2, or 3 groups independently selected from the group consisting of R_{205} , $-\text{CO}_2\text{H}$, and $-\text{CO}_2\text{-(C}_1\text{-C}_4\text{ alkyl)}$; $-(\text{CR}_{245}\text{R}_{250})_{0-4}\text{-aryl}$; $-(\text{CR}_{245}\text{R}_{250})_{0-4}\text{-heteroaryl}$; $-(\text{CR}_{245}\text{R}_{250})_{0-4}\text{-heterocycloalkyl}$; $-(\text{CR}_{245}\text{R}_{250})_{0-4}\text{-aryl-heteroaryl}$; $-(\text{CR}_{245}\text{R}_{250})_{0-4}\text{-aryl-heterocycloalkyl}$;
- 20 $-(\text{CR}_{245}\text{R}_{250})_{0-4}\text{-aryl-aryl}$; $-(\text{CR}_{245}\text{R}_{250})_{0-4}\text{-heteroaryl-aryl}$; $-(\text{CR}_{245}\text{R}_{250})_{0-4}\text{-heteroaryl-heterocycloalkyl}$; $-(\text{CR}_{245}\text{R}_{250})_{0-4}\text{-heteroaryl-heteroaryl}$; $-(\text{CR}_{245}\text{R}_{250})_{0-4}\text{-heterocycloalkyl-heteroaryl}$; $-(\text{CR}_{245}\text{R}_{250})_{0-4}\text{-heterocycloalkyl-heterocycloalkyl}$; $-(\text{CR}_{245}\text{R}_{250})_{0-4}\text{-heterocycloalkyl-aryl}$;
- 25 $-\text{[C(R}_{255}\text{)(R}_{260}\text{)]}_{1-3}\text{-CO-N-(R}_{255}\text{)}_2$; $-\text{CH(aryl)}_2$; $-\text{CH(heteroaryl)}_2$; $-\text{CH(heterocycloalkyl)}_2$; $-\text{CH(aryl)(heteroaryl)}$; cyclopentyl, cyclohexyl, or cycloheptyl ring fused to aryl, heteroaryl, or heterocycloalkyl wherein one carbon of the cyclopentyl, cyclohexyl, or cycloheptyl is
- 30 optionally replaced with NH , NR_{215} , O , or S(=O)_{0-2} , and wherein the cyclopentyl, cyclohexyl, or cycloheptyl group can be optionally substituted with 1 or 2 groups that are independently R_{205} or $=\text{O}$; $-\text{CO-NR}_{235}\text{R}_{240}$; $-\text{SO}_2\text{-(C}_1\text{-C}_4\text{ alkyl)}$; $\text{C}_2\text{-C}_{10}$ alkenyl optionally substituted with 1, 2, or 3 R_{205}

groups; C₂-C₁₀ alkynyl optionally substituted with 1, 2, or 3 R₂₀₅ groups; -(CH₂)₀₋₁-CH((CH₂)₀₋₆-OH)-(CH₂)₀₋₁-aryl; -(CH₂)₀₋₁-CHRC₆-(CH₂)₀₋₁-heteroaryl; -CH(-aryl or -heteroaryl)-CO-O(C₁-C₄ alkyl); -CH(-CH₂-OH)-CH(OH)-phenyl-NO₂; (C₁-C₆ alkyl)-O-(C₁-C₆ alkyl)-OH; -CH₂-NH-CH₂-CH(-O-CH₂-CH₃)₂; -H; and -(CH₂)₀₋₆-C(=NR₂₃₅)(NR₂₃₅R₂₄₀); wherein

each aryl is optionally substituted with 1, 2, or 3 R₂₀₀; each heteroaryl is optionally substituted with 1, 2, 3, or 4 R₂₀₀;

each heterocycloalkyl is optionally substituted with 1, 2, 3, or 4 R₂₁₀;

R₂₀₀ at each occurrence is independently selected from the group consisting of C₁-C₆ alkyl optionally substituted with 1, 2, or 3 R₂₀₅ groups; OH; -NO₂; halogen; -CO₂H; C≡N; -(CH₂)₀₋₄-CO-NR₂₂₀R₂₂₅; -(CH₂)₀₋₄-CO-(C₁-C₁₂ alkyl); -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkenyl); -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkynyl); -(CH₂)₀₋₄-CO-(C₃-C₇ cycloalkyl); -(CH₂)₀₋₄-CO-aryl; -(CH₂)₀₋₄-CO-heteroaryl; -(CH₂)₀₋₄-CO-heterocycloalkyl; -(CH₂)₀₋₄-CO₂R₂₁₅; -(CH₂)₀₋₄-SO₂-NR₂₂₀R₂₂₅; -(CH₂)₀₋₄-SO-(C₁-C₈ alkyl); -(CH₂)₀₋₄-SO₂-(C₁-C₁₂ alkyl); -(CH₂)₀₋₄-SO₂-(C₃-C₇ cycloalkyl); -(CH₂)₀₋₄-N(H or R₂₁₅)-CO₂R₂₁₅; -(CH₂)₀₋₄-N(H or R₂₁₅)-CO-N(R₂₁₅)₂; -(CH₂)₀₋₄-N-CS-N(R₂₁₅)₂; -(CH₂)₀₋₄-N(-H or R₂₁₅)-CO-R₂₂₀; -(CH₂)₀₋₄-NR₂₂₀R₂₂₅; -(CH₂)₀₋₄-O-CO-(C₁-C₆ alkyl); -(CH₂)₀₋₄-O-P(O)-(OR₂₄₀)₂; -(CH₂)₀₋₄-O-CO-N(R₂₁₅)₂; -(CH₂)₀₋₄-O-CS-N(R₂₁₅)₂; -(CH₂)₀₋₄-O-(R₂₁₅)₂; -(CH₂)₀₋₄-O-(R₂₁₅)₂-COOH; -(CH₂)₀₋₄-S-(R₂₁₅)₂; -(CH₂)₀₋₄-O-(C₁-C₆ alkyl optionally substituted with 1, 2, 3, or 5 -F); C₃-C₇ cycloalkyl; C₂-C₆ alkenyl optionally substituted with 1 or 2 R₂₀₅ groups; C₂-C₆ alkynyl optionally substituted with 1 or 2 R₂₀₅ groups; -(CH₂)₀₋₄-N(H or R₂₁₅)-SO₂-R₂₂₀; and -(CH₂)₀₋₄-C₃-C₇ cycloalkyl;

wherein each aryl group at each occurrence is optionally substituted with 1, 2, or 3 groups

that are independently R_{205} , R_{210} or C_1-C_6 alkyl substituted with 1, 2, or 3 groups that are independently R_{205} or R_{210} ;

wherein each heterocycloalkyl group at each occurrence is optionally substituted with 1, 2, or 3 groups that are independently R_{210} ;

wherein each heteroaryl group at each occurrence is optionally substituted with 1, 2, or 3 groups that are independently R_{205} , R_{210} , or C_1-C_6 alkyl substituted with 1, 2, or 3 groups that are independently R_{205} or R_{210} ;

R_{205} at each occurrence is independently selected from the group consisting of C_1-C_6 alkyl, halogen, $-OH$, $-O-$, phenyl, $-SH$, $-C\equiv N$, $-CF_3$, C_1-C_6 alkoxy, NH_2 , $NH(C_1-C_6$ alkyl), and $N-(C_1-C_6$ alkyl)(C_1-C_6 alkyl);

R_{210} at each occurrence is independently selected from the group consisting of C_1-C_6 alkyl optionally substituted with 1, 2, or 3 R_{205} groups; C_2-C_6 alkenyl optionally substituted with 1, 2, or 3 R_{205} groups; C_2-C_6 alkynyl optionally substituted with 1, 2, or 3 R_{205} groups; halogen; C_1-C_6 alkoxy; C_1-C_6 haloalkoxy; $-NR_{220}R_{225}$; OH ; $C\equiv N$; C_3-C_7 cycloalkyl optionally substituted with 1, 2, or 3 R_{205} groups; $-CO-(C_1-C_4$ alkyl); $-SO_2-NR_{235}R_{240}$; $-CO-NR_{235}R_{240}$; $-SO_2-(C_1-C_4$ alkyl); and $=O$; wherein

R_{215} at each occurrence is independently selected from the group consisting of C_1-C_6 alkyl, $-(CH_2)_{0-2}-(aryl)$, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, and $-(CH_2)_{0-2}-(heteroaryl)$, $-(CH_2)_{0-2}-(heterocycloalkyl)$; wherein the aryl group at each occurrence is optionally substituted with 1, 2, or 3 groups that are independently R_{205} or R_{210} ; wherein the heterocycloalkyl group at each occurrence is optionally substituted with 1, 2, or 3 R_{210} ; wherein

each heteroaryl group at each occurrence is optionally substituted with 1, 2, or 3 R₂₁₀;

R₂₂₀ and R₂₂₅ at each occurrence are independently selected from the group consisting of -H, -C₁-C₆ alkyl, hydroxy C₁-C₆ alkyl, amino C₁-C₆ alkyl; halo C₁-C₆ alkyl; -C₃-C₇ cycloalkyl, -(C₁-C₂ alkyl)-(C₃-C₇ cycloalkyl), -(C₁-C₆ alkyl)-O-(C₁-C₃ alkyl), -C₂-C₆ alkenyl, -C₂-C₆ alkynyl, -C₁-C₆ alkyl chain with one double bond and one triple bond, -aryl, -heteroaryl, and -heterocycloalkyl; wherein the aryl group at each occurrence is optionally substituted with 1, 2, or 3 R₂₇₀ groups, wherein

R₂₇₀ at each occurrence is independently R₂₀₅, C₁-C₆ alkyl optionally substituted with 1, 2, or 3 R₂₀₅ groups; C₂-C₆ alkenyl optionally substituted with 1, 2, or 3 R₂₀₅ groups; C₂-C₆ alkynyl optionally substituted with 1, 2, or 3 R₂₀₅ groups; halogen; C₁-C₆ alkoxy; C₁-C₆ haloalkoxy; NR₂₃₅R₂₄₀; OH; C≡N; C₃-C₇ cycloalkyl optionally substituted with 1, 2, or 3 R₂₀₅ groups; -CO-(C₁-C₄ alkyl); -SO₂-NR₂₃₅R₂₄₀; -CO-NR₂₃₅R₂₄₀; -SO₂-(C₁-C₄ alkyl); and =O; wherein the heterocycloalkyl group at each occurrence is optionally substituted with 1, 2, or 3 R₂₀₅ groups; wherein each heteroaryl group at each occurrence is optionally substituted with 1, 2, or 3 R₂₀₅ groups;

R₂₃₅ and R₂₄₀ at each occurrence are independently H, or C₁-C₆ alkyl;

R₂₄₅ and R₂₅₀ at each occurrence are independently selected from the group consisting of H, C₁-C₄ alkyl, C₁-C₄ hydroxyalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, -(CH₂)₀₋₄-C₃-C₇ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, aryl C₁-C₄ alkyl, heteroaryl C₁-C₄ alkyl, and phenyl; or

R₂₄₅ and R₂₅₀ are taken together with the carbon to which they are attached to form a carbocycle of 3, 4, 5, 6,

or 7 carbon atoms, optionally where one carbon atom is replaced by a heteroatom selected from the group consisting of -O-, -S-, -SO₂-, and -NR₂₂₀-;

R₂₅₅ and R₂₆₀ at each occurrence are independently selected

5 from the group consisting of H; C₁-C₆ alkyl optionally substituted with 1, 2, or 3 R₂₀₅ groups; C₂-C₆ alkenyl optionally substituted with 1, 2, or 3 R₂₀₅ groups; C₂-C₆ alkynyl optionally substituted with 1, 2, or 3 R₂₀₅ groups; -(CH₂)₁₋₂-S(O)₀₋₂-(C₁-C₆ alkyl);
10 -(CH₂)₀₋₄-C₃-C₇ cycloalkyl optionally substituted with 1, 2, or 3 R₂₀₅ groups; -(C₁-C₄ alkyl)-aryl; -(C₁-C₄ alkyl)-heteroaryl; -(C₁-C₄ alkyl)-heterocycloalkyl; -aryl; -heteroaryl; -heterocycloalkyl; -(CH₂)₁₋₄-R₂₆₅-
15 (CH₂)₀₋₄-aryl; -(CH₂)₁₋₄-R₂₆₅-(CH₂)₀₋₄-heteroaryl; and; -(CH₂)₁₋₄-R₂₆₅-(CH₂)₀₋₄-heterocycloalkyl; wherein R₂₆₅ at each occurrence is independently -O-, -S- or -N(C₁-C₆ alkyl)-;

each aryl or phenyl is optionally substituted with 1, 2, or 3 groups that are independently R₂₀₅, R₂₁₀,
20 or C₁-C₆ alkyl substituted with 1, 2, or 3 groups that are independently R₂₀₅ or R₂₁₀;

each heteroaryl is optionally substituted with 1, 2, 3, or 4 R₂₀₀, each heterocycloalkyl is optionally substituted with 1, 2, 3, or 4 R₂₁₀.

25

The invention also encompasses methods for the treatment or prevention of Alzheimer's disease, mild cognitive impairment Down's syndrome, Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, cerebral amyloid angiopathy,
30 other degenerative dementias, dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, diffuse Lewy body type of Alzheimer's disease comprising

administration of a therapeutically effective amount of a compound or salt of formula X, to a patient in need thereof.

Preferably, the patient is a human.

More preferably, the disease is Alzheimer's disease.

5 More preferably, the disease is dementia.

The invention also provides pharmaceutical compositions comprising a compound or salt of formula X and at least one pharmaceutically acceptable carrier, solvent, adjuvant or
10 diluent.

The invention also provides the use of a compound or salt according to formula X for the manufacture of a medicament.

The invention also provides the use of a compound or salt of formula X for the treatment or prevention of Alzheimer's
15 disease, mild cognitive impairment Down's syndrome, Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, cerebral amyloid angiopathy, other degenerative dementias, dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with
20 progressive supranuclear palsy, dementia associated with cortical basal degeneration, or diffuse Lewy body type of Alzheimer's disease.

The invention also provides compounds, pharmaceutical
25 compositions, kits, and methods for inhibiting beta-secretase-mediated cleavage of amyloid precursor protein (APP). More particularly, the compounds, compositions, and methods of the invention are effective to inhibit the production of A-beta peptide and to treat or prevent any human or veterinary disease
30 or condition associated with a pathological form of A-beta peptide.

The compounds, compositions, and methods of the invention are useful for treating humans who have Alzheimer's Disease (AD), for helping prevent or delay the onset of AD, for

treating patients with mild cognitive impairment (MCI), and preventing or delaying the onset of AD in those patients who would otherwise be expected to progress from MCI to AD, for treating Down's syndrome, for treating Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch Type, for treating cerebral beta-amyloid angiopathy and preventing its potential consequences such as single and recurrent lobar hemorrhages, for treating other degenerative dementias, including dementias of mixed vascular and degenerative origin, for treating dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, and diffuse Lewy body type AD, and for treating frontotemporal dementias with parkinsonism (FTDP).

The compounds of the invention possess beta-secretase inhibitory activity. The inhibitory activities of the compounds of the invention is readily demonstrated, for example, using one or more of the assays described herein or known in the art.

Unless the substituents for a particular formula are expressly defined for that formula, they are understood to carry the definitions set forth in connection with the preceeding formula to which the particular formula makes reference.

The invention also provides methods of preparing the compounds of the invention and the intermediates used in those methods.

Detailed Description of the Invention

As noted above, the invention provides compound of Formula X.

In alternate aspects of the invention, R_5 is a C_3 - C_8 cycloalkyl optionally substituted with one or two groups that are C_1 - C_6 alkyl, more preferably C_1 - C_2 alkyl, C_1 - C_6 alkoxy, more preferably C_1 - C_2 alkoxy, CF_3 , OH, NH_2 , $NH(C_1$ - C_6 alkyl), $N(C_1$ - C_6 alkyl)(C_1 - C_6 alkyl), halogen, CN, or NO_2 .

In this aspect, preferred R_5 groups are C_3 - C_6 cycloalkyl groups optionally substituted with 2, more preferably 1 group selected from methyl, ethyl, OH, halogen, preferably F or Cl, methoxy or ethoxy. Other preferred R_5 groups within this aspect are C_3 - C_6 cycloalkyl groups substituted with 1 or 2 groups that are independently CF_3 , Cl, F, methyl, ethyl or cyano.

Preferred compounds of formula X include those of formula X-I, i.e., compounds of formula X wherein

R_1 is $(CH_2)_{n_1}-(R_{1-aryl})$ where n_1 is zero or one and R_{1-aryl} is phenyl optionally substituted with 1, 2, 3, or 4 groups independently selected from C_1 - C_6 alkyl optionally substituted with 1, 2, or 3 substituents selected from the group consisting of C_1 - C_3 alkyl, halogen, -OH, -SH, - $NR_{1-a}R_{1-b}$, - $C\equiv N$, - CF_3 , and C_1 - C_3 alkoxy; halogen; C_1 - C_6 alkoxy; - $NR_{N-2}R_{N-3}$; and OH; wherein R_{N-2} and R_{N-3} at each occurrence are independently selected from the group consisting of - C_1 - C_8 alkyl optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of -OH, - NH_2 , phenyl and halogen; - C_3 - C_8 cycloalkyl; -(C_1 - C_2 alkyl)-(C_3 - C_8 cycloalkyl); -(C_1 - C_6 alkyl)-O-(C_1 - C_3 alkyl); - C_2 - C_6 alkenyl; - C_2 - C_6 alkynyl; - C_1 - C_6 alkyl chain with one double bond and one triple bond; aryl; heteroaryl; heterocycloalkyl;

or

R_{N-2} , R_{N-3} and the nitrogen to which they are attached form a 5, 6, or 7 membered heterocycloalkyl or heteroaryl group, wherein said heterocycloalkyl or heteroaryl group is optionally fused to a benzene, pyridine, or pyrimidine ring, and said groups are unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that at each occurrence are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, halo C_1-C_6 alkyl, halo C_1-C_6 alkoxy, -CN, $-NO_2$, $-NH_2$, $NH(C_1-C_6 \text{ alkyl})$, $N(C_1-C_6 \text{ alkyl})(C_1-C_6 \text{ alkyl})$, -OH, $-C(O)NH_2$, $-C(O)NH(C_1-C_6 \text{ alkyl})$, $-C(O)N(C_1-C_6 \text{ alkyl})(C_1-C_6 \text{ alkyl})$, C_1-C_6 alkoxy C_1-C_6 alkyl, C_1-C_6 thioalkoxy, and C_1-C_6 thioalkoxy C_1-C_6 alkyl.

More preferred compounds of formula X-I include those of formula X-II, i.e., compounds of formula X-I wherein R_2 and R_3 are independently selected from H or C_1-C_6 alkyl optionally substituted with 1, 2, or 3 substituents selected from the group consisting of C_1-C_3 alkyl, halogen, -OH, -SH, $-C\equiv N$, $-CF_3$, C_1-C_3 alkoxy, and $-NR_{1-a}R_{1-b}$.

Preferred compounds of formula X-II include those wherein R_C is selected from the group consisting of C_1-C_{10} alkyl optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of R_{205} , $-OC=ONR_{235}R_{240}$, $-S(=O)_{0-2}(C_1-C_6 \text{ alkyl})$, -SH, $-NR_{235}C=ONR_{235}R_{240}$, $-C=ONR_{235}R_{240}$, and $-S(=O)_2NR_{235}R_{240}$; $-(CH_2)_{0-3}-(C_3-C_8)$ cycloalkyl wherein the cycloalkyl is optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of R_{205} , $-CO_2H$, and $-CO_2-(C_1-C_4 \text{ alkyl})$; $-(CR_{245}R_{250})_{0-4}\text{-aryl}$; $-(CR_{245}R_{250})_{0-4}\text{-heteroaryl}$; $-(CR_{245}R_{250})_{0-4}\text{-heterocycloalkyl}$; $-[C(R_{255})(R_{260})]_{1-3}\text{-CO-N-}(R_{255})_2$; $-CH(aryl)_2$; $-CH(heteroaryl)_2$; $-CH(heterocycloalkyl)_2$; $-CH(aryl)(heteroaryl)$; $-CO-$

NR₂₃₅R₂₄₀; -(CH₂)₀₋₁-CH((CH₂)₀₋₆-OH)-(CH₂)₀₋₁-aryl; -(CH₂)₀₋₁-CHR_{C-6}-(CH₂)₀₋₁-heteroaryl; -CH(-aryl or -heteroaryl)-CO-O(C₁-C₄ alkyl); -CH(-CH₂-OH)-CH(OH)-phenyl-NO₂; (C₁-C₆ alkyl)-O-(C₁-C₆ alkyl)-OH; -CH₂-NH-CH₂-CH(-O-CH₂-CH₃)₂; -H; and -(CH₂)₀₋₆-C(=NR₂₃₅)(NR₂₃₅R₂₄₀); wherein each aryl is optionally substituted with 1, 2, or 3 R₂₀₀; each heteroaryl is optionally substituted with 1, 2, 3, or

4 R₂₀₀;

each heterocycloalkyl is optionally substituted with 1, 2, 3, or 4 R₂₁₀;

R₂₀₀ at each occurrence is independently selected from the group consisting of C₁-C₆ alkyl optionally substituted with 1, 2, or 3 R₂₀₅ groups; OH; -NO₂; halogen; -CO₂H; C≡N; -(CH₂)₀₋₄-CO-NR₂₂₀R₂₂₅; -(CH₂)₀₋₄-CO-(C₁-C₁₂ alkyl); -(CH₂)₀₋₄-CO₂R₂₁₅; and -(CH₂)₀₋₄-O-(C₁-C₆ alkyl optionally substituted with 1, 2, 3, or 5 -F); wherein each aryl group at each occurrence is optionally substituted with 1, 2, or 3 groups that are independently R₂₀₅, R₂₁₀ or C₁-C₆ alkyl substituted with 1, 2, or 3 groups that are independently R₂₀₅ or R₂₁₀;

wherein each heterocycloalkyl group at each occurrence is optionally substituted with 1, 2, or 3 groups that are independently R₂₁₀;

wherein each heteroaryl group at each occurrence is optionally substituted with 1, 2, or 3 groups that are independently R₂₀₅, R₂₁₀, or C₁-C₆ alkyl substituted with 1, 2, or 3 groups that are independently R₂₀₅ or R₂₁₀;

R₂₀₅ at each occurrence is independently selected from the group consisting of C₁-C₆ alkyl, halogen, -OH, -O-phenyl, -SH, -C≡N, -CF₃, C₁-C₆ alkoxy, NH₂, NH(C₁-C₆ alkyl), and N-(C₁-C₆ alkyl)(C₁-C₆ alkyl);

5 R₂₁₀ at each occurrence is independently selected from the group consisting of C₁-C₆ alkyl optionally substituted with 1, 2, or 3 R₂₀₅ groups; halogen; C₁-C₆ alkoxy; C₁-C₆ haloalkoxy; -NR₂₂₀R₂₂₅; OH; C≡N; C₃-C₇ cycloalkyl optionally substituted with 1, 2, or 3 R₂₀₅ groups; -CO-(C₁-C₄ alkyl); -SO₂-NR₂₃₅R₂₄₀; -CO-NR₂₃₅R₂₄₀; -SO₂-(C₁-C₄ alkyl); and =O; wherein

10 R₂₁₅ at each occurrence is independently selected from the group consisting of C₁-C₆ alkyl, -(CH₂)₀₋₂-(aryl), C₃-C₇ cycloalkyl, and -(CH₂)₀₋₂-(heteroaryl), -(CH₂)₀₋₂-(heterocycloalkyl); wherein the aryl group at each occurrence is optionally substituted with 1, 2, or 3 groups that are independently R₂₀₅ or R₂₁₀; wherein the heterocycloalkyl group at each occurrence is
15 optionally substituted with 1, 2, or 3 R₂₁₀; wherein each heteroaryl group at each occurrence is optionally substituted with 1, 2, or 3 R₂₁₀;

20 R₂₂₀ and R₂₂₅ at each occurrence are independently selected from the group consisting of -H, -C₁-C₆ alkyl, hydroxy C₁-C₆ alkyl, amino C₁-C₆ alkyl; halo C₁-C₆ alkyl; -C₃-C₇ cycloalkyl, -(C₁-C₆ alkyl)-O-(C₁-C₃ alkyl), -aryl, -heteroaryl, and -heterocycloalkyl; wherein the aryl group at each occurrence is optionally substituted with 1, 2, or 3 R₂₇₀ groups,
25 each heteroaryl is optionally substituted with 1, 2, 3, or 4 R₂₀₀, each heterocycloalkyl is optionally substituted with 1, 2, 3, or 4 R₂₁₀ wherein

30 R₂₇₀ at each occurrence is independently R₂₀₅, C₁-C₆ alkyl optionally substituted with 1, 2, or 3 R₂₀₅ groups; halogen; C₁-C₆ alkoxy; C₁-C₆ haloalkoxy; NR₂₃₅R₂₄₀; OH; C≡N; -CO-(C₁-C₄ alkyl); and =O; wherein the heterocycloalkyl group at each occurrence is optionally substituted with 1, 2, or 3 R₂₀₅ groups;

wherein each heteroaryl group at each occurrence is optionally substituted with 1, 2, or 3 R_{205} groups;

R_{235} and R_{240} at each occurrence are independently H, or C_1 - C_6 alkyl;

5 R_{245} and R_{250} at each occurrence are independently selected from the group consisting of H, C_1 - C_4 alkyl, C_1 - C_4 hydroxyalkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy, or

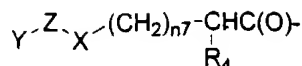
R_{245} and R_{250} are taken together with the carbon to which they are attached to form a carbocycle of 3, 4, 5, 6,
10 or 7 carbon atoms, wherein the carbocycle is optionally substituted with 1 or 2 groups that are independently OH, methyl, Cl, F, OCH_3 , CF_3 , NO_2 , or CN;

R_{255} and R_{260} at each occurrence are independently selected
15 from the group consisting of H; C_1 - C_6 alkyl optionally substituted with 1, 2, or 3 R_{205} groups; $-(CH_2)_{0-4}-C_3-C_7$ cycloalkyl optionally substituted with 1, 2, or 3 R_{205} groups; $-(C_1-C_4$ alkyl)-aryl; $-(C_1-C_4$ alkyl)-heteroaryl; $-(C_1-C_4$ alkyl)-heterocycloalkyl;
20 aryl; heteroaryl; heterocycloalkyl; $-(CH_2)_{1-4}-R_{265}-$ $(CH_2)_{0-4}$ -aryl; $-(CH_2)_{1-4}-R_{265}-(CH_2)_{0-4}$ -heteroaryl; and; $-(CH_2)_{1-4}-R_{265}-(CH_2)_{0-4}$ -heterocycloalkyl; wherein R_{265} at each occurrence is independently -O-, -S- or -
 $N(C_1-C_6$ alkyl)-;

25 each aryl or phenyl is optionally substituted with 1, 2, or 3 groups that are independently R_{205} , R_{210} , or C_1 - C_6 alkyl substituted with 1, 2, or 3 groups that are independently R_{205} or R_{210} .

30 Other preferred compounds of formulas X-I and X-II include compounds of formula X-III, i.e., those of formulas X-I or X-II wherein

R_N is:



wherein

R₄ is NH₂; -NH-(CH₂)_{n₆}-R₄₋₁; -NHR₈; -NR₅₀C(O)R₅; or -NR₅₀CO₂R₅₁;

wherein

5 n₆ is 0, 1, 2, or 3;

n₇ is 0, 1, 2, or 3;

R₄₋₁ is selected from the group consisting of -SO₂-(C₁-C₈ alkyl), -SO-(C₁-C₈ alkyl), -S-(C₁-C₈ alkyl), -S-CO-(C₁-C₆ alkyl), -SO₂-NR₄₋₂R₄₋₃; -CO-C₁-C₂ alkyl; -CO-NR₄₋
10 ₃R₄₋₄;

R₄₋₂ and R₄₋₃ are independently H, C₁-C₃ alkyl, or C₃-C₆ cycloalkyl;

R₄₋₄ is alkyl, phenylalkyl, C₂-C₄ alkanoyl, or phenylalkanoyl;

15 R₅ is cyclopropyl; cyclobutyl; cyclopentyl; and cyclohexyl; wherein each cycloalkyl group is optionally substituted with one or two groups that are C₁-C₆ alkyl, more preferably C₁-C₂ alkyl, C₁-C₆ alkoxy, more preferably C₁-C₂ alkoxy, CF₃, OH, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)(C₁-C₆ alkyl), halogen, CN, or NO₂; or the cycloalkyl group is
20 substituted with 1 or 2 groups that are independently CF₃, Cl, F, methyl, ethyl or cyano; C₁-C₆ alkyl optionally substituted with 1, 2, or 3 groups that are independently halogen, -NR₆R₇, C₁-C₄ alkoxy, C₅-C₆ heterocycloalkyl, C₅-C₆ heteroaryl, phenyl, C₃-C₇ cycloalkyl, -S-C₁-C₄ alkyl, -SO₂-
25 C₁-C₄ alkyl, -CO₂H, -CONR₆R₇, -CO₂-C₁-C₄ alkyl, or phenyloxy; heteroaryl optionally substituted with 1, 2, or 3 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, C₁-C₄ haloalkyl, or OH; heterocycloalkyl
30 optionally substituted with 1, 2, or 3 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, or C₂-C₄ alkanoyl; phenyl optionally substituted with 1, 2, 3, or 4

groups that are independently halogen, OH, C₁-C₄ alkyl, C₁-C₄ alkoxy, or C₁-C₄ haloalkyl; and -NR₆R₇; wherein R₆ and R₇ are independently selected from the group

consisting of H, C₁-C₆ alkyl, C₂-C₆ alkanoyl, phenyl, -SO₂-C₁-C₄ alkyl, and phenyl C₁-C₄ alkyl;

R₈ is selected from the group consisting of -SO₂-heteroaryl optionally substituted with 1 or 2 groups that are independently C₁-C₄ alkyl or halogen; -SO₂-aryl, -SO₂-heterocycloalkyl, -C(O)NHR₉, heterocycloalkyl, -S-C₂-C₄ alkanoyl, wherein R₉ is phenyl C₁-C₄ alkyl, C₁-C₆ alkyl, or H;

R₅₀ is H or C₁-C₆ alkyl;

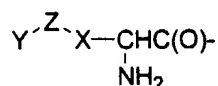
R₅₁ is selected from the group consisting of phenyl C₁-C₄ alkyl; C₁-C₆ alkyl optionally substituted with 1, 2, or 3 groups that are independently halogen, cyano, -NR₆R₇, -C(O)NR₆R₇, C₃-C₇ or -C₁-C₄ alkoxy; heterocycloalkyl optionally substituted with 1 or 2 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, C₂-C₄ alkanoyl, phenyl C₁-C₄ alkyl, and -SO₂ C₁-C₄ alkyl; heterocycloalkylalkyl optionally substituted with 1 or 2 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, C₂-C₄ alkanoyl, phenyl C₁-C₄ alkyl, and -SO₂ C₁-C₄ alkyl; alkenyl; alkynyl; heteroaryl optionally substituted with 1, 2, or 3 groups that are independently OH, C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, NH₂, NH(C₁-C₆ alkyl) or N(C₁-C₆ alkyl)(C₁-C₆ alkyl); heteroarylalkyl optionally substituted with 1, 2, or 3 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, NH₂, NH(C₁-C₆ alkyl) or N(C₁-C₆ alkyl)(C₁-C₆ alkyl); phenyl; C₃-C₈ cycloalkyl, and cycloalkylalkyl, wherein the phenyl; C₃-C₈ cycloalkyl, and cycloalkylalkyl groups are optionally substituted with 1, 2, 3, 4 or 5 groups that are independently halogen, CN, NO₂, C₁-C₆

alkyl, C₁-C₆ alkoxy, C₂-C₆ alkanoyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, hydroxy, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy C₁-C₆ alkyl, C₁-C₆ thioalkoxy, C₁-C₆ thioalkoxy C₁-C₆ alkyl, or C₁-C₆ alkoxy C₁-C₆ alkoxy.

5

Preferred compounds of formula X-III include compounds wherein

R_N is



10 wherein

X is C₁-C₄ alkylidenyl optionally optionally substituted with 1, 2, or 3 methyl groups; or -NR₄₋₆-; or

R₄ and R₄₋₆ combine to form -(CH₂)_{n10}-, wherein

n₁₀ is 1, 2, 3, or 4;

15 Z is selected from a bond; SO₂; SO; S; and C(O);

Y is selected from H; C₁-C₄ haloalkyl; C₅-C₆ heterocycloalkyl containing at least one N, O, or S; phenyl; OH;

-N(Y₁)(Y₂); C₁-C₁₀ alkyl optionally substituted with 1 thru 3 substituents which can be the same or different and are selected from halogen, hydroxy, alkoxy, thioalkoxy, and haloalkoxy; C₃-C₈ cycloalkyl optionally substituted with 1, 2, or 3 groups independently selected from C₁-C₃ alkyl, and halogen; alkoxy; phenyl optionally substituted with halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, CN or NO₂; phenyl C₁-C₄ alkyl optionally substituted with halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, CN or NO₂; wherein

25 Y₁ and Y₂ are the same or different and are H; C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 substituents selected from the group consisting of halogen, C₁-C₄ alkoxy, C₃-C₈ cycloalkyl, and OH; C₂-C₆ alkenyl; C₂-C₆ alkanoyl; phenyl; -SO₂-C₁-C₄ alkyl; phenyl C₁-C₄ alkyl; and C₃-C₈ cycloalkyl C₁-C₄ alkyl; or

-N(Y₁)(Y₂) forms a ring selected from piperazinyl,
piperidinyl, morpholinyl, and pyrrolidinyl, wherein
each ring is optionally substituted with 1, 2, 3, or
4 groups that are independently C₁-C₆ alkyl, C₁-C₆
5 alkoxy, C₁-C₆ alkoxy C₁-C₆ alkyl, or halogen; and
R₂₀ at each occurrence is independently selected from hydrogen,
C₁-C₆ alkyl, C₁-C₆ alkoxy C₁-C₆ alkyl, halo C₁-C₆ alkyl, C₁-
C₆ alkanoyl, each of which is unsubstituted or substituted
with 1, or 2 groups independently selected from halogen,
10 C₁-C₆ alkyl, hydroxy, C₁-C₆ alkoxy, NH₂, and -R₂₆-R₂₇,
wherein
R₂₆ is selected from -C(O)-, -SO₂-, -CO₂-, -C(O)NH-, and
-C(O)N(C₁-C₆ alkyl)-; and
R₂₇ is selected from the group consisting of C₁-C₆ alkyl,
15 C₁-C₆ alkoxy, aryl C₁-C₆ alkyl, heterocycloalkyl, and
heteroaryl, wherein each of the above is
unsubstituted or substituted with 1, 2, 3, 4, or 5
groups that are independently C₁-C₄ alkyl, C₁-C₄
alkoxy, halogen, halo C₁-C₆ alkyl, hydroxy C₁-C₆
20 alkyl, -C(O)NH₂, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆
alkyl)(C₁-C₆ alkyl), -C(O)NH(C₁-C₆ alkyl), or -
C(O)N(C₁-C₆ alkyl)(C₁-C₆ alkyl).

More preferred compounds of formula X-III include
25 compounds wherein
X is C₁-C₄ alkylidenyl optionally optionally substituted with
1, 2, or 3 methyl groups;
Z is selected from SO₂; SO; S; and C(O);
Y is selected from H; C₁-C₄ haloalkyl; C₅-C₆ heterocycloalkyl
30 containing at least one N, O, or S; phenyl; OH; -
N(Y₁)(Y₂); C₁-C₁₀ alkyl optionally substituted with 1 thru
3 substituents which can be the same or different and are
selected from the group consisting of halogen, hydroxy,
alkoxy, thioalkoxy, and haloalkoxy; C₃-C₈ cycloalkyl

optionally substituted with 1, 2, or 3 groups
independently selected from C₁-C₃ alkyl, and halogen;
alkoxy; phenyl optionally substituted with halogen, C₁-C₄
alkyl, C₁-C₄ alkoxy, CN or NO₂; phenyl C₁-C₄ alkyl
5 optionally substituted with halogen, C₁-C₄ alkyl, C₁-C₄
alkoxy, CN or NO₂; wherein

Y₁ and Y₂ are the same or different and are H; C₁-C₆ alkyl
optionally substituted with 1, 2, or 3 substituents
selected from the group consisting of halogen, C₁-C₄
10 alkoxy, C₃-C₈ cycloalkyl, and OH; C₂-C₆ alkenyl; C₂-C₆
alkanoyl; phenyl; -SO₂-C₁-C₄ alkyl; phenyl C₁-C₄
alkyl; or C₃-C₈ cycloalkyl C₁-C₄ alkyl; or

-N(Y₁)(Y₂) forms a ring selected from piperazinyll,
piperidinyl, morpholinyl, and pyrrolidinyl, wherein
15 each ring is optionally substituted with 1, 2, 3, or
4 groups that are independently C₁-C₆ alkyl, C₁-C₆
alkoxy, C₁-C₆ alkoxy C₁-C₆ alkyl, or halogen;

R₂₀ at each occurrence is independently hydrogen, C₁-C₆ alkyl,
C₁-C₄ alkoxy C₁-C₆ alkyl, halo C₁-C₆ alkyl, C₂-C₆ alkanoyl,
20 each of which is unsubstituted or substituted with 1 or 2
groups independently selected from halogen, hydroxy, C₁-C₆
alkoxy, and NH₂.

Even more preferred compounds of formula X-III include
25 compounds wherein

R_C is C₁-C₈ alkyl optionally substituted with 1, 2, or 3 groups
independently selected from the group consisting of R₂₀₅,
-OC=ONR₂₃₅R₂₄₀, -S(=O)₀₋₂(C₁-C₆ alkyl), -SH, -C=ONR₂₃₅R₂₄₀, and
-S(=O)₂NR₂₃₅R₂₄₀; -(CH₂)₀₋₃-(C₃-C₈) cycloalkyl wherein the
30 cycloalkyl is optionally substituted with 1, 2, or 3
groups independently selected from the group consisting of
R₂₀₅, -CO₂H, and -CO₂-(C₁-C₄ alkyl); -(CR₂₄₅R₂₅₀)₀₋₄-phenyl;
-(CR₂₄₅R₂₅₀)₀₋₄-heteroaryl; -(CR₂₄₅R₂₅₀)₀₋₄-heterocycloalkyl;
-(CH₂)₀₋₁-CH((CH₂)₀₋₄-OH)-(CH₂)₀₋₁-phenyl; -(CH₂)₀₋₁-CHR_{C-6}-

$(\text{CH}_2)_{0-1}$ -heteroaryl; $-\text{CH}(-\text{CH}_2-\text{OH})-\text{CH}(\text{OH})$ -phenyl- NO_2 ; $(\text{C}_1-\text{C}_6$ alkyl)- $\text{O}-(\text{C}_1-\text{C}_6$ alkyl)- OH ; or $-(\text{CH}_2)_{0-6}-\text{C}(=\text{NR}_{235})(\text{NR}_{235}\text{R}_{240})$; wherein

each aryl is optionally substituted with 1, 2, or 3 R_{200} ;

5 each heteroaryl is optionally substituted with 1, 2, 3, or 4 R_{200} ;

each heterocycloalkyl is optionally substituted with 1, 2, 3, or 4 R_{210} ;

10 R_{200} at each occurrence is independently C_1-C_6 alkyl optionally substituted with 1, 2, or 3 R_{205} groups; OH ; $-\text{NO}_2$; halogen; $-\text{CO}_2\text{H}$; $\text{C}\equiv\text{N}$; $-(\text{CH}_2)_{0-4}-\text{CO}-\text{NR}_{220}\text{R}_{225}$; $-(\text{CH}_2)_{0-4}-\text{CO}-(\text{C}_1-\text{C}_{12}$ alkyl); $-(\text{CH}_2)_{0-4}-\text{CO}_2\text{R}_{215}$; or $-(\text{CH}_2)_{0-4}-\text{O}-(\text{C}_1-\text{C}_6$ alkyl optionally substituted with 1, 2, 3, or 5 $-\text{F}$);

15 R_{205} at each occurrence is independently C_1-C_6 alkyl, halogen, $-\text{OH}$, $-\text{O}$ -phenyl, $-\text{SH}$, $-\text{C}\equiv\text{N}$, $-\text{CF}_3$, C_1-C_6 alkoxy, NH_2 , $\text{NH}(\text{C}_1-\text{C}_6$ alkyl), or $\text{N}-(\text{C}_1-\text{C}_6$ alkyl)(C_1-C_6 alkyl);

20 R_{210} at each occurrence is independently C_1-C_6 alkyl optionally substituted with 1, 2, or 3 R_{205} groups; halogen; C_1-C_6 alkoxy; C_1-C_6 haloalkoxy; $-\text{NR}_{220}\text{R}_{225}$; OH ; $\text{C}\equiv\text{N}$; C_3-C_7 cycloalkyl optionally substituted with 1, 2, or 3 R_{205} groups; $-\text{CO}-(\text{C}_1-\text{C}_4$ alkyl); $-\text{SO}_2-\text{NR}_{235}\text{R}_{240}$; $-\text{CO}-\text{NR}_{235}\text{R}_{240}$; $-\text{SO}_2-(\text{C}_1-\text{C}_4$ alkyl); and $=\text{O}$; wherein

25 R_{215} at each occurrence is independently C_1-C_6 alkyl, $-(\text{CH}_2)_{0-2}-(\text{phenyl})$, C_3-C_7 cycloalkyl, and $-(\text{CH}_2)_{0-2}-(\text{heteroaryl})$, $-(\text{CH}_2)_{0-2}-(\text{heterocycloalkyl})$; wherein the phenyl group at each occurrence is optionally substituted with 1, 2, or 3 groups that are
30 independently R_{205} or R_{210} ; wherein the heterocycloalkyl group at each occurrence is optionally substituted with 1, 2, or 3 R_{210} ; wherein each heteroaryl group at each occurrence is optionally substituted with 1, 2, or 3 R_{210} ;

R₂₂₀ and R₂₂₅ at each occurrence are independently -H, -C₁-C₆ alkyl, hydroxy C₁-C₆ alkyl, halo C₁-C₆ alkyl; -C₃-C₇ cycloalkyl, and -(C₁-C₆ alkyl)-O-(C₁-C₃ alkyl);

5 R₂₃₅ and R₂₄₀ at each occurrence are independently H, or C₁-C₆ alkyl;

R₂₄₅ and R₂₅₀ at each occurrence are independently H, C₁-C₄ alkyl, C₁-C₄ hydroxyalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, or

10 R₂₄₅ and R₂₅₀ are taken together with the carbon to which they are attached to form a carbocycle of 3, 4, 5, 6, or 7 carbon atoms.

Still yet even more preferred compounds of formula X-III include compounds wherein

15 R₁ is benzyl which is optionally substituted with 1, 2, 3, or 4 groups independently selected from halogen, C₁-C₄ alkoxy, hydroxy, and C₁-C₄ alkyl optionally substituted with 1, 2, or 3 substituents halogen, OH, SH, NH₂, NH(C₁-C₆ alkyl), N-(C₁-C₆ alkyl)(C₁-C₆ alkyl), C≡N, CF₃;

20 R₂ and R₃ are independently selected from H or C₁-C₄ alkyl optionally substituted with 1 substituent selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, NH₂, NH(C₁-C₆ alkyl), and NH(C₁-C₆ alkyl)(C₁-C₆ alkyl);

25 R₂₀ at each occurrence is independently hydrogen, C₁-C₆ alkyl, C₁-C₂ alkoxy C₁-C₄ alkyl, halo C₁-C₄ alkyl, C₂-C₆ alkanoyl, each of which is unsubstituted or substituted with 1 or 2 groups independently selected from halogen, hydroxy, and NH₂;

30 R_C is C₁-C₈ alkyl optionally substituted with 1, 2, or 3 groups independently selected from R₂₀₅, -SH, -C=ONR₂₃₅R₂₄₀, and -S(=O)₂NR₂₃₅R₂₄₀; -(CH₂)₀₋₃-(C₃-C₆) cycloalkyl wherein the cycloalkyl is optionally substituted with 1, 2, or 3 groups independently selected from R₂₀₅, -CO₂H, and -CO₂-(C₁-C₄ alkyl); -(CR₂₄₅R₂₅₀)₀₋₄-phenyl optionally substituted

with 1, 2, or 3 R_{200} ; $-(CR_{245}R_{250})_{0-3}$ -pyridyl; $-(CR_{245}R_{250})_{0-3}$ -pyridazinyl; $-(CR_{245}R_{250})_{0-3}$ -pyrimidinyl; $-(CR_{245}R_{250})_{0-3}$ -pyrazinyl; $-(CR_{245}R_{250})_{0-3}$ -furyl; $-(CR_{245}R_{250})_{0-3}$ -indolyl; $-(CR_{245}R_{250})_{0-3}$ -thienyl; $-(CR_{245}R_{250})_{0-3}$ -pyrrolyl; $-(CR_{245}R_{250})_{0-3}$ -pyrazolyl; $(CR_{245}R_{250})_{0-3}$ -benzoxazolyl; $-(CR_{245}R_{250})_{0-3}$ -imidazolyl; each of the above heteroaryl groups is optionally substituted with 1, 2, 3, or 4 R_{200} ; $-(CR_{245}R_{250})_{0-3}$ -imidazolidinyl; $(CR_{245}R_{250})_{0-3}$ -tetrahydrofuryl; $(CR_{245}R_{250})_{0-3}$ -tetrahydropyranyl; $(CR_{245}R_{250})_{0-3}$ -piperazinyl; $(CR_{245}R_{250})_{0-3}$ -pyrrolidinyl; $(CR_{245}R_{250})_{0-3}$ -piperidinyl; $(CR_{245}R_{250})_{0-3}$ -indolinyl; each of the above heterocycloalkyl groups is optionally substituted with 1, 2, 3, or 4 R_{210} ; $(CH_2)_{0-1}$ -CH $((CH_2)_{0-4}$ -OH)- $(CH_2)_{0-1}$ -phenyl; $-(CH_2)_{0-1}$ -CH(C_1 - C_4 hydroxyalkyl)- $(CH_2)_{0-1}$ -pyridyl;

R_{200} at each occurrence is independently C_1 - C_6 alkyl optionally substituted with 1, 2, or 3 R_{205} groups; OH; $-NO_2$; halogen; $-CO_2H$; $C\equiv N$; $-(CH_2)_{0-4}$ -CO- $NR_{220}R_{225}$; $-(CH_2)_{0-4}$ -CO- $(C_1-C_8$ alkyl); $-(CH_2)_{0-4}$ -CO $_2R_{215}$; and $-(CH_2)_{0-4}$ -O- $(C_1-C_6$ alkyl optionally substituted with 1, 2, 3, or 5 -F);

R_{205} at each occurrence is independently C_1 - C_6 alkyl, halogen, -OH, -O-phenyl, -SH, $-C\equiv N$, $-CF_3$, C_1 - C_6 alkoxy, NH_2 , $NH(C_1-C_6$ alkyl), and $N-(C_1-C_6$ alkyl)(C_1-C_6 alkyl);

R_{210} at each occurrence is independently C_1 - C_6 alkyl optionally substituted with 1 or 2 R_{205} groups; halogen; C_1 - C_4 alkoxy; C_1 - C_4 haloalkoxy; $-NR_{220}R_{225}$; OH; $C\equiv N$; C_3 - C_7 cycloalkyl optionally substituted with 1 or 2 R_{205} groups; $-CO-(C_1-C_4$ alkyl); $-SO_2-NR_{235}R_{240}$; $-CO-NR_{235}R_{240}$; $-SO_2-(C_1-C_4$ alkyl); and =O; wherein

R_{215} at each occurrence is independently C_1 - C_6 alkyl, $-(CH_2)_{0-2}$ -(phenyl), C_3 - C_6 cycloalkyl, $-(CH_2)_{0-2}$ -(pyridyl), $-(CH_2)_{0-2}$ -(pyrrolyl), $-(CH_2)_{0-2}$ -(imidazolyl), $-(CH_2)_{0-2}$ -(pyrimidyl), $-(CH_2)_{0-2}$ -

- (pyrrolidinyl), $-(CH_2)_{0-2}-(\text{imidazolidinyl})$ $-(CH_2)_{0-2}-(\text{piperazinyl})$, $-(CH_2)_{0-2}-(\text{piperidinyl})$, and $-(CH_2)_{0-2}-(\text{morpholinyl})$; wherein the phenyl group at each occurrence is optionally substituted with 1 or 2 groups that are independently R_{205} or R_{210} ; wherein each heterocycloalkyl group at each occurrence is optionally substituted with 1 or 2 R_{210} ; wherein each heteroaryl group at each occurrence is optionally substituted with 1 or 2 R_{210} ;
- 5 R_{220} and R_{225} at each occurrence are independently $-H$, $-C_1-C_4$ alkyl, hydroxy C_1-C_4 alkyl, halo C_1-C_4 alkyl; $-C_3-C_6$ cycloalkyl, and $-(C_1-C_4 \text{ alkyl})-O-(C_1-C_2 \text{ alkyl})$;
- 10 R_{235} and R_{240} at each occurrence are independently H , or C_1-C_6 alkyl;
- 15 R_{245} and R_{250} at each occurrence are independently H , C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, or
- R_{245} and R_{250} are taken together with the carbon to which they are attached to form a carbocycle of 3, 4, 5, or
- 20 6 carbon atoms.

Other more preferred compounds of formula X-III include compounds wherein

- X is $-C_1-C_3$ alkylidenyl optionally optionally substituted with 1
- 25 or 2 methyl groups;
- Z is SO_2 ; SO ; S ; or $C(O)$;
- Y is C_1-C_4 haloalkyl; OH ; $-N(Y_1)(Y_2)$; C_1-C_{10} alkyl optionally substituted with 1 or 2 substituents which can be the same or different and are selected from halogen, hydroxy, C_1-C_4 alkoxy, C_1-C_4 thioalkoxy, and C_1-C_4 haloalkoxy; C_1-C_4 alkoxy; phenyl optionally substituted with halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, CN or NO_2 ; and benzyl optionally substituted with halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, CN or NO_2 ; wherein
- 30

Y₁ and Y₂ are the same or different and are H; C₁-C₆ alkyl optionally substituted with 1, 2, or 3 substituents selected from halogen, C₁-C₂ alkoxy, C₃-C₆ cycloalkyl, and OH; C₂-C₆ alkanoyl; phenyl; -SO₂-C₁-C₄ alkyl; benzyl; and C₃-C₆ cycloalkyl C₁-C₂ alkyl; or -N(Y₁)(Y₂) forms a ring selected from piperazinyl, piperidinyl, morpholinyl, and pyrrolidinyl, wherein each ring is optionally substituted with 1, 2, 3, or 4 groups that are independently C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkoxy C₁-C₆ alkyl, or halogen.

Other even more preferred compounds of formula X-III include those of formula X-IV, i.e., compounds of formula X-III. wherein

X is -C₁-C₃ alkylidenyl optionally optionally substituted with 1 methyl group;

Z is SO₂; SO; S; or C(O);

Y is OH; -N(Y₁)(Y₂); phenyl; benzyl; or C₁-C₁₀ alkyl optionally substituted with 1 or 2 substituents which can be the same or different and are selected from halogen, hydroxy, methoxy, ethoxy, thiomethoxy, thioethoxy, and CF₃; wherein Y₁ and Y₂ are the same or different and are H; C₁-C₄ alkyl optionally substituted with 1 or 2 substituents selected from halogen, methoxy, ethoxy, cyclopropyl, and OH; or

-N(Y₁)(Y₂) forms a ring selected from piperazinyl, piperidinyl, morpholinyl, and pyrrolidinyl, wherein each ring is optionally substituted with 1 or 2 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, or halogen;

R₁ is benzyl which is optionally substituted with 1, 2, or 3 groups independently selected from methyl, ethyl, n-propyl, isopropyl, hydroxymethyl, monohalomethyl, dihalomethyl, trihalomethyl, -CH₂CF₃, methoxymethyl,

halogen, methoxy, ethoxy, n-propyloxy, isopropyloxy, and
OH;

R₂ and R₃ are independently H or C₁-C₄ alkyl;

R₂₀ at each occurrence is independently hydrogen, C₁-C₄ alkyl,
5 or C₂-C₄ alkanoyl;

R_C is C₁-C₆ alkyl optionally substituted with 1, 2, or 3 R₂₀₅

groups; cyclopropyl, cyclopropylmethyl, cyclopentyl,
cyclopentylmethyl, cyclohexyl, cyclohexylmethyl;

10 -(CR₂₄₅R₂₅₀)₀₋₃-phenyl optionally substituted with 1 or 2 R₂₀₀
groups; -(CR₂₄₅R₂₅₀)₀₋₃-pyridyl optionally substituted with 1
or 2 R₂₀₀; -(CR₂₄₅R₂₅₀)₀₋₃-piperazinyl; or (CR₂₄₅R₂₅₀)₀₋₃-
pyrrolidinyl; -(CR₂₄₅R₂₅₀)₀₋₃-piperidinyl; each of the above
heterocycloalkyl groups is optionally substituted with 1
or 2 R₂₁₀ groups;

15 R₂₀₀ at each occurrence is independently selected from C₁-
C₄ alkyl optionally substituted with 1 or 2 R₂₀₅
groups; OH; and halogen;

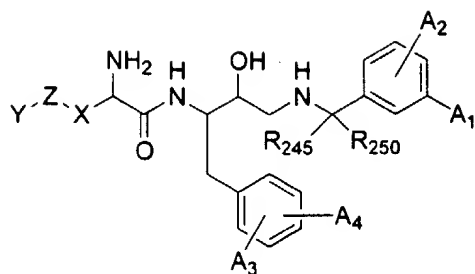
R₂₀₅ at each occurrence is independently selected from C₁-
C₄ alkyl, halogen, -OH, -SH, -C≡N, -CF₃, and C₁-C₄
20 alkoxy;

R₂₁₀ at each occurrence is independently selected from C₁-
C₄ alkyl optionally substituted with 1 or 2 R₂₀₅
groups; halogen; C₁-C₄ alkoxy; OCF₃; NH₂, NH(C₁-C₆
alkyl); N(C₁-C₆ alkyl)(C₁-C₆ alkyl); OH; and -CO-(C₁-C₄
25 alkyl); wherein

R₂₄₅ and R₂₅₀ at each occurrence are independently selected
from H, C₁-C₄ hydroxyalkyl, C₁-C₄ alkoxy, or

R₂₄₅ and R₂₅₀ are taken together with the carbon to which
they are attached to form a carbocycle of 3, 5, or 6
30 carbon atoms.

Preferred compounds of formula X-IV include those of
formula X-IV-a:



X-IV-a

wherein X, Y, Z, R₂₄₅, and R₂₅₀ are as defined for formula X-IV;

A₁ and A₂ are independently H, methyl, ethyl, propyl, methoxy,

5 F, Cl, Br, I, or CF₃;

A₃ and A₄ are independently F, Cl, Br, I, methyl, methoxy, or
H;

R₂₄₅ and R₂₅₀ are taken together with the carbon to which they
are attached to form a carbocycle of 3, 5, or 6 carbon
10 atoms.

More preferred compounds of formula X-IV-a include those
wherein

A₂ is H;

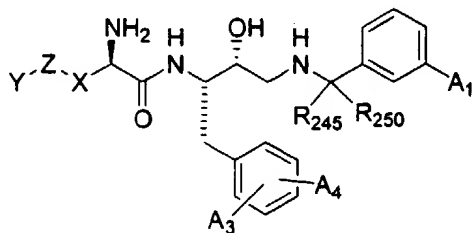
15 A₃ and A₄ are independently H, F, Cl, Br, or I;

X is C₁ or C₂ alkylidenyl;

Z is SO₂, SO, or S; and

Y is phenyl, or C₁-C₁₁ alkyl. More preferably, Y is methyl,
propyl, n-butyl, isobutyl, isopentyl, 4-heptyl, 3-heptyl,
20 3-pentyl, or 5-nonyl.

Even more preferred compounds of formula X-IV include
those of formula X-IV-b:



X-IV-b

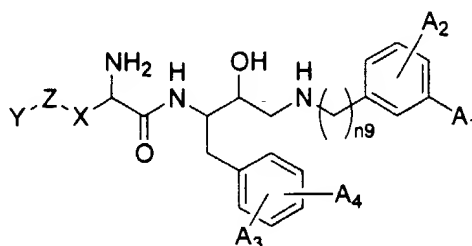
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wherein A₁, X, Y, Z, R₂₄₅, and R₂₅₀ are as defined for formula X-IV;

A₃ and A₄ are independently H, F, Cl, methyl, ethyl, methoxy, ethoxy, CF₃ or OCF₃.

5

Other preferred compounds of formula X-IV include those of formula X-V wherein



X-V

10 wherein

n₉ is 1 or 2;

A₁ and A₂ are independently H, methyl, ethyl, propyl, methoxy, ethoxy, F, Cl, Br, I, CF₃, OCF₃, or C₂-C₆ alkynyl; and

A₃ and A₄ are independently F, Cl, Br, I, methyl, methoxy, or

15 H.

Preferred compounds of formula X-V include those wherein A₁ is C₁-C₂ alkyl, preferably ethyl, or C₂-C₃ alkynyl. More preferably A₁ is ethyl, I, or C₂ alkynyl;

20 A₂ is H;

A₃ and A₄ are independently H, F, Cl, Br, or I;

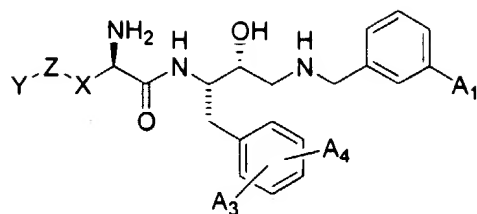
X is C₁ or C₂ alkylidenyl;

Z is SO₂; SO; or S; and

Y is phenyl, methyl, propyl, n-butyl, isobutyl, isopentyl, 4-

25 heptyl, 3-heptyl, 3-pentyl, or 5-nonyl.

More preferred compounds of formula X-V include those of formula X-V-a



formula X-V-a

wherein

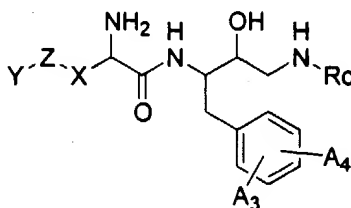
A₃ and A₄ are independently H, F, or Cl.

5

Other preferred compounds of formula X-IV include those of formula X-VI, i.e., compounds of formula X-IV wherein R_c is C₃-C₈ alkyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or -(C₁-C₄ alkyl)-cyclopropyl. Even more preferred R_c is n-butyl, isobutyl, n-pentyl, isopentyl, n-hexyl, isohexyl, cyclopropyl, or cyclopropylmethyl.

10

Preferred compounds of formula X-VI include those of formula X-VI-a:



X-VI-a

wherein

A₃ and A₄ are independently halogen, methyl, ethyl, n-propyl, iso-propyl, methoxy, ethoxy, n-propoxy, iso-propoxy, or H;

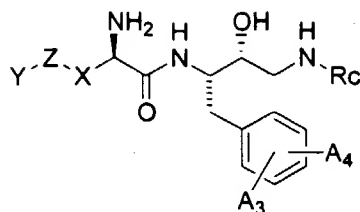
20 X is C₁ or C₂ alkylidenyl;

Z is SO₂; SO; or S; and

Y is phenyl, or C₁-C₁₀ alkyl. Even more preferred is when Y is methyl, propyl, n-butyl, isobutyl, isopentyl, 4-heptyl, 3-heptyl, 3-pentyl, or 5-nonyl.

25

More preferred compounds of formula X-VI include those of formula X-VI-b:



X-VI-b

wherein

A₃ and A₄ are independently H, F, Cl, methyl, or methoxy.

5

Representative compounds of formula X-III wherein R₄ is NH₂ are

S-butyl-N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-D-cysteinamide;

3-(butylsulfinyl)-N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-D-alaninamide;

3-(butylsulfonyl)-N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-D-alaninamide;

3-(butylsulfonyl)-N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-L-alaninamide;

3-(butylsulfonyl)-N-1--[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-(isopentylamino)propyl]-D-alaninamide;

N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(1-(3-ethylphenyl)cyclopropyl)amino]-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]-L-alaninamide;

N-1--[(1S,2R)-3-(cyclopropylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N-1--[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxypropyl-3-(isopentylamino)]-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N-1--{(1S,2S)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]alaninamide;

Other preferred compounds of formula X-II include those of formula X-VII, i.e., compounds of formula X-II wherein

$$Y-Z-X-(CH_2)_{n7}-\underset{\substack{| \\ R_{50}-N-CO_2R_{51}}}{CHC(O)-}\}_{}$$

R₅₀ is H or C₁-C₆ alkyl;

with 1, 2, or 3 groups that are independently halogen, cyano, $-NR_6R_7$, $-C(O)NR_6R_7$, or $-C_1-C_4$ alkoxy; heterocycloalkyl optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, C_2-C_4 alkanoyl, phenyl C_1-C_4 alkyl, and $-SO_2$ C_1-C_4 alkyl; heterocycloalkylalkyl optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, C_2-C_4 alkanoyl, phenyl C_1-C_4 alkyl, and $-SO_2$ C_1-C_4 alkyl; alkenyl; alkynyl; heteroaryl optionally substituted with 1, 2, or 3 groups that are independently OH, C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, NH_2 , $NH(C_1-C_6$ alkyl) or $N(C_1-C_6$ alkyl)(C_1-C_6 alkyl); heteroarylalkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, NH_2 , $NH(C_1-C_6$ alkyl) or $N(C_1-C_6$ alkyl)(C_1-C_6 alkyl); phenyl; C_3-C_8 cycloalkyl; or cycloalkylalkyl; wherein the phenyl, C_3-C_8 cycloalkyl, and cycloalkylalkyl groups are optionally substituted with 1, 2, 3, 4 or 5 groups that are independently halogen, CN, NO_2 , C_1-C_6 alkyl, C_1-C_6 alkoxy, C_2-C_6 alkanoyl, C_1-C_6

haloalkyl, C₁-C₆ haloalkoxy, hydroxy, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy C₁-C₆ alkyl, C₁-C₆ thioalkoxy, C₁-C₆ thioalkoxy C₁-C₆ alkyl, or C₁-C₆ alkoxy C₁-C₆ alkoxy;

5 R₆ and R₇ are independently H, C₁-C₆ alkyl, C₂-C₆ alkanoyl, phenyl, -SO₂-C₁-C₄ alkyl, or phenyl C₁-C₄ alkyl;

X is C₁-C₄ alkylidenyl optionally optionally substituted with 1, 2, or 3 methyl groups; or -NR₄₋₆-; or

10 R₄ and R₄₋₆ combine to form -(CH₂)_{n10}-, wherein n₁₀ is 1, 2, 3, or 4;

Z is a bond; SO₂; SO; S; or C(O);

Y is H; C₁-C₄ haloalkyl; C₅-C₆ heterocycloalkyl containing at least one N, O, or S; phenyl; OH; -N(Y₁)(Y₂); C₁-C₁₀ alkyl... optionally substituted with 1 thru 3 substituents which
15 can be the same or different and are selected from halogen, hydroxy, alkoxy, thioalkoxy, and haloalkoxy; C₃-C₈ cycloalkyl optionally substituted with 1, 2, or 3 groups independently selected from C₁-C₃ alkyl, and halogen; alkoxy; phenyl optionally substituted with
20 halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, CN or NO₂; or phenyl C₁-C₄ alkyl optionally substituted with halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, CN or NO₂; wherein

Y₁ and Y₂ are the same or different and are H; C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 substituents
25 selected from halogen, C₁-C₄ alkoxy, C₃-C₈ cycloalkyl, and OH; C₂-C₆ alkenyl; C₂-C₆ alkanoyl; phenyl; -SO₂-C₁-C₄ alkyl; phenyl C₁-C₄ alkyl; or C₃-C₈ cycloalkyl C₁-C₄ alkyl; or

-N(Y₁)(Y₂) forms a ring selected from piperazinyl,
30 piperidinyl, morpholinyl, and pyrrolidinyl, wherein each ring is optionally substituted with 1, 2, 3, or 4 groups that are independently C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkoxy C₁-C₆ alkyl, or halogen;

R₂₀ at each occurrence is independently hydrogen, C₁-C₆ alkyl, C₁-C₆ alkoxy C₁-C₆ alkyl, halo C₁-C₆ alkyl, or C₁-C₆ alkanoyl, each of which is unsubstituted or substituted with 1, or 2 groups independently selected from halogen, C₁-C₆ alkyl, hydroxy, C₁-C₆ alkoxy, NH₂, and -R₂₆-R₂₇,
5 wherein

R₂₆ is -C(O)-, -SO₂-, -CO₂-, -C(O)NH-, or -C(O)N(C₁-C₆ alkyl)-;

R₂₇ is C₁-C₆ alkyl, C₁-C₆ alkoxy, aryl C₁-C₆ alkyl,

10 heterocycloalkyl, or heteroaryl, wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, halo C₁-C₆ alkyl, hydroxy C₁-C₆ alkyl, -C(O)NH₂, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)(C₁-C₆ alkyl), -C(O)NH(C₁-C₆ alkyl), or -
15 C(O)N(C₁-C₆ alkyl)(C₁-C₆ alkyl).

Preferred compounds of formula X-VII include those wherein:

20 R₂ and R₃ are independently H or C₁-C₆ alkyl optionally substituted with 1, or 2 substituents selected from halogen, -OH, -SH, -C≡N, -CF₃, and C₁-C₃ alkoxy;

n₇ is 0, 1, or 2;

R₅₀ is H or C₁-C₄ alkyl;

25 R₅₁ is selected from benzyl; phenethyl; C₁-C₆ alkyl optionally substituted with 1, 2, or 3 groups that are independently halogen, cyano, -NR₆R₇, -C(O)NR₆R₇, or -C₁-C₄ alkoxy; heterocycloalkyl containing at least one N, O, or S and optionally substituted with 1 or 2 groups that are
30 independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, C₂-C₄ alkanoyl, phenyl C₁-C₄ alkyl, and -SO₂ C₁-C₄ alkyl; heterocycloalkylalkyl containing at least one N, O, or S and optionally substituted with 1 or 2 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, C₂-C₄

alkanoyl, phenyl C₁-C₄ alkyl, and -SO₂ C₁-C₄ alkyl; C₂-C₆ alkenyl; C₂-C₆ alkynyl; heteroaryl optionally substituted with 1, 2, or 3 groups that are independently OH, C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, NH₂, NH(C₁-C₆ alkyl) or N(C₁-C₆ alkyl)(C₁-C₆ alkyl); heteroarylalkyl containing at least one N, O, or S and optionally substituted with 1, 2, or 3 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, NH₂, NH(C₁-C₆ alkyl) or N(C₁-C₆ alkyl)(C₁-C₆ alkyl); phenyl; C₃-C₆ cycloalkyl, and C₃-C₆ cycloalkyl C₁-C₄ alkyl, wherein the phenyl; C₃-C₆ cycloalkyl, and C₃-C₆ cycloalkyl C₁-C₄ alkyl groups are optionally substituted with 1, 2, or 3 groups that are independently halogen, CN, NO₂, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₂-C₆ alkanoyl, C₁-C₄ haloalkyl, C₁-C₄ haloalkoxy, hydroxy, C₁-C₄ hydroxyalkyl, C₁-C₄ thioalkoxy;

R₆ and R₇ are independently H, C₁-C₆ alkyl, C₂-C₆ alkanoyl, phenyl, -SO₂-C₁-C₄ alkyl, benzyl or phenethyl;

X is -C₁-C₄ alkylidenyl optionally optionally substituted with 1 or 2 methyl groups;

Z is SO₂; SO; S; or C(O);

Y is H; C₁-C₄ haloalkyl; C₅-C₆ heterocycloalkyl containing at least one N, O, or S; phenyl; OH; -N(Y₁)(Y₂); C₁-C₁₀ alkyl optionally substituted with 1 thru 3 substituents which can be the same or different and are selected from the group consisting of halogen, hydroxy, C₁-C₄ alkoxy, C₁-C₄ thioalkoxy, and C₁-C₄ haloalkoxy; C₃-C₆ cycloalkyl optionally substituted with 1 group selected from C₁-C₃ alkyl, and halogen; C₁-C₄ alkoxy; phenyl optionally substituted with halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, CN or NO₂; or phenyl C₁-C₄ alkyl optionally substituted with halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, CN or NO₂; wherein Y₁ and Y₂ are the same or different and are H; C₁-C₁₀ alkyl optionally substituted with 1, or 2 substituents selected from halogen, C₁-C₄ alkoxy, C₃-C₆ cycloalkyl,

and OH; C₂-C₆ alkanoyl; phenyl; -SO₂-C₁-C₄ alkyl;
phenyl C₁-C₄ alkyl; or C₃-C₈ cycloalkyl C₁-C₄ alkyl; or
-N(Y₁)(Y₂) forms a ring selected from piperazinyl,
piperidinyl, morpholinyl, and pyrrolidinyl, wherein
5 each ring is optionally substituted with 1, 2, or 3
groups that are independently C₁-C₄ alkyl, C₁-C₄
alkoxy, C₁-C₄ alkoxy C₁-C₄ alkyl, or halogen;

R₂₀ at each occurrence is independently hydrogen, C₁-C₄ alkyl,
halo C₁-C₄ alkyl, or C₂-C₄ alkanoyl, each of which is
10 unsubstituted or substituted with 1, or 2 groups
independently selected from halogen, C₁-C₄ alkyl, hydroxy,
C₁-C₄ alkoxy, NH₂, and -R₂₆-R₂₇; wherein
R₂₆ is -C(O)-, -SO₂-, or -CO₂-;

R₂₇ is C₁-C₆ alkyl, benzyl, or phenethyl, wherein each of
15 the above is unsubstituted or substituted with 1, 2,
or 3 groups that are independently C₁-C₄ alkyl, C₁-C₄
alkoxy, halogen, CF₃, or hydroxy C₁-C₄ alkyl.

More preferred compounds of formula X-VII include those
20 wherein:

R_C is C₁-C₈ alkyl optionally substituted with 1, 2, or 3 groups
independently selected from the group consisting of R₂₀₅,
-OC=ONR₂₃₅R₂₄₀, -S(=O)₀₋₂(C₁-C₆ alkyl), -SH, -C=ONR₂₃₅R₂₄₀, and
-S(=O)₂NR₂₃₅R₂₄₀; -(CH₂)₀₋₃-(C₃-C₈) cycloalkyl wherein the
25 cycloalkyl is optionally substituted with 1, 2, or 3
groups independently selected from the group consisting of
R₂₀₅, -CO₂H, and -CO₂-(C₁-C₄ alkyl); -(CR₂₄₅R₂₅₀)₀₋₄-phenyl;
-(CR₂₄₅R₂₅₀)₀₋₄-heteroaryl; -(CR₂₄₅R₂₅₀)₀₋₄-heterocycloalkyl; or
-(CH₂)₀₋₁-CH(C₁-C₄ hydroxyalkyl)-(CH₂)₀₋₁-heteroaryl; wherein
30 each aryl is optionally substituted with 1, 2, or 3 R₂₀₀;
each heteroaryl is optionally substituted with 1, 2, 3, or
4 R₂₀₀;

each heterocycloalkyl is optionally substituted with 1, 2,
3, or 4 R₂₁₀;

R₂₀₀ at each occurrence is independently C₁-C₆ alkyl optionally substituted with 1, 2, or 3 R₂₀₅ groups; OH; -NO₂; halogen; -CO₂H; C≡N; -(CH₂)₀₋₄-CO-NR₂₂₀R₂₂₅; -(CH₂)₀₋₄-CO-(C₁-C₁₂ alkyl); -(CH₂)₀₋₄-CO₂R₂₁₅; or -(CH₂)₀₋₄-O-(C₁-C₆ alkyl optionally substituted with 1, 2, 3, or 5 -F);

R₂₀₅ at each occurrence is independently C₁-C₆ alkyl, halogen, -OH, -O-phenyl, -SH, -C≡N, -CF₃, C₁-C₆ alkoxy, NH₂, NH(C₁-C₆ alkyl), or N-(C₁-C₆ alkyl)(C₁-C₆ alkyl);

R₂₁₀ at each occurrence is independently C₁-C₆ alkyl optionally substituted with 1, 2, or 3 R₂₀₅ groups; halogen; C₁-C₆ alkoxy; C₁-C₆ haloalkoxy; -NR₂₂₀R₂₂₅; OH; C≡N; C₃-C₇ cycloalkyl optionally substituted with 1, 2, or 3 R₂₀₅ groups; -CO-(C₁-C₄ alkyl); -SO₂-NR₂₃₅R₂₄₀; -CO-NR₂₃₅R₂₄₀; -SO₂-(C₁-C₄ alkyl); or =O; wherein

R₂₁₅ at each occurrence is independently C₁-C₆ alkyl, -(CH₂)₀₋₂-(phenyl), C₃-C₇ cycloalkyl, and -(CH₂)₀₋₂-(heteroaryl), or -(CH₂)₀₋₂-(heterocycloalkyl); wherein the phenyl group at each occurrence is optionally substituted with 1, 2, or 3 groups that are independently R₂₀₅ or R₂₁₀; wherein the heterocycloalkyl group at each occurrence is optionally substituted with 1, 2, or 3 R₂₁₀; wherein each heteroaryl group at each occurrence is optionally substituted with 1, 2, or 3 R₂₁₀;

R₂₂₀ and R₂₂₅ at each occurrence are independently -H, -C₁-C₆ alkyl, hydroxy C₁-C₄ alkyl, halo C₁-C₄ alkyl; -C₃-C₇ cycloalkyl, or -(C₁-C₆ alkyl)-O-(C₁-C₃ alkyl);

R₂₃₅ and R₂₄₀ at each occurrence are independently H, or C₁-C₆ alkyl;

R₂₄₅ and R₂₅₀ at each occurrence are independently H, C₁-C₄ alkyl, C₁-C₄ hydroxyalkyl, C₁-C₄ alkoxy, or C₁-C₄ haloalkoxy, or

R₂₄₅ and R₂₅₀ are taken together with the carbon to which they are attached to form a carbocycle of 3, 4, 5, or 6 carbon atoms.

5 Even more preferred compounds of formula X-VII include those wherein:

R₁ is benzyl which is optionally substituted with 1, 2, 3, or 4 groups independently selected from C₁-C₄ alkyl optionally substituted with 1, or 2 substituents selected from
10 halogen, -OH, -SH, NH₂, NH(C₁-C₆ alkyl), N-(C₁-C₆ alkyl)(C₁-C₆ alkyl), -C≡N, -CF₃, and C₁-C₃ alkoxy; halogen; C₁-C₄ alkoxy; and OH;

R₂₀ at each occurrence is independently hydrogen, C₁-C₆ alkyl, C₁-C₂ alkoxy C₁-C₄ alkyl, C₂-C₆ alkanoyl, each of which is
15 unsubstituted or substituted with 1 or 2 groups independently selected from halogen, hydroxy, C₁-C₄ alkoxy, and NH₂;

R_C is C₁-C₈ alkyl optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of R₂₀₅, -
20 SH, -C=ONR₂₃₅R₂₄₀, and -S(=O)₂NR₂₃₅R₂₄₀; -(CH₂)₀₋₃-(C₃-C₆) cycloalkyl wherein the cycloalkyl is optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of R₂₀₅, -CO₂H, and -CO₂-(C₁-C₄ alkyl); -(CR₂₄₅R₂₅₀)₀₋₄-phenyl optionally substituted with 1,
25 2, or 3 R₂₀₀; -(CR₂₄₅R₂₅₀)₀₋₃-pyridyl; -(CR₂₄₅R₂₅₀)₀₋₃-pyridazinyl; -(CR₂₄₅R₂₅₀)₀₋₃-pyrimidinyl; -(CR₂₄₅R₂₅₀)₀₋₃-pyrazinyl; -(CR₂₄₅R₂₅₀)₀₋₃-furyl; -(CR₂₄₅R₂₅₀)₀₋₃-indolyl; -(CR₂₄₅R₂₅₀)₀₋₃-thienyl; -(CR₂₄₅R₂₅₀)₀₋₃-pyrrolyl; -(CR₂₄₅R₂₅₀)₀₋₃-pyrazolyl; (CR₂₄₅R₂₅₀)₀₋₃-benzoxazolyl; -(CR₂₄₅R₂₅₀)₀₋₃-
30 imidazolyl; each of the above heteroaryl groups is optionally substituted with 1, 2, 3, or 4 R₂₀₀; -(CR₂₄₅R₂₅₀)₀₋₃-imidazolidinyl; (CR₂₄₅R₂₅₀)₀₋₃-tetrahydrofuryl; (CR₂₄₅R₂₅₀)₀₋₃-tetrahydropyranyl; (CR₂₄₅R₂₅₀)₀₋₃-piperazinyl; (CR₂₄₅R₂₅₀)₀₋₃-pyrrolidinyl; (CR₂₄₅R₂₅₀)₀₋₃-piperidinyl; (CR₂₄₅R₂₅₀)₀₋₃-

indoliny1; each of the above heterocycloalkyl groups is optionally substituted with 1, 2, 3, or 4 R_{210} ; $(CH_2)_{0-1}-CH((CH_2)_{0-4}-OH)-(CH_2)_{0-1}$ -phenyl; or $-(CH_2)_{0-1}-CH(C_1-C_4$ hydroxyalkyl) $-(CH_2)_{0-1}$ -pyridyl;

5 R_{200} at each occurrence is independently C_1-C_6 alkyl optionally substituted with 1, 2, or 3 R_{205} groups; OH; $-NO_2$; halogen; $-CO_2H$; $C\equiv N$; $-(CH_2)_{0-4}-CO-NR_{220}R_{225}$; $-(CH_2)_{0-4}-CO-(C_1-C_8$ alkyl); $-(CH_2)_{0-4}-CO_2R_{215}$; or $-(CH_2)_{0-4}-O-(C_1-C_6$ alkyl optionally substituted with 1, 2, 3, 10 or 5 $-F$);

R_{205} at each occurrence is independently C_1-C_6 alkyl, halogen, $-OH$, $-O$ -phenyl, $-SH$, $-C\equiv N$, $-CF_3$, C_1-C_6 alkoxy, NH_2 , $NH(C_1-C_6$ alkyl), or $N-(C_1-C_6$ alkyl)(C_1-C_6 alkyl);

15 R_{210} at each occurrence is independently C_1-C_6 alkyl optionally substituted with 1 or 2 R_{205} groups; halogen; C_1-C_4 alkoxy; C_1-C_4 haloalkoxy; $-NR_{220}R_{225}$; OH; $C\equiv N$; C_3-C_7 cycloalkyl optionally substituted with 1 or 2 R_{205} groups; $-CO-(C_1-C_4$ alkyl); $-SO_2-NR_{235}R_{240}$; $-CO-$ 20 $NR_{235}R_{240}$; $-SO_2-(C_1-C_4$ alkyl); or $=O$; wherein

R_{215} at each occurrence is independently C_1-C_6 alkyl, $-(CH_2)_{0-2}-(phenyl)$, C_3-C_6 cycloalkyl, $-(CH_2)_{0-2}-(pyridyl)$, $-(CH_2)_{0-2}-(pyrrolyl)$, $-(CH_2)_{0-2}-(imidazolyl)$, $-(CH_2)_{0-2}-(pyrimidyl)$, $-(CH_2)_{0-2}-(pyrrolidinyl)$, $-(CH_2)_{0-2}-(imidazolidinyl)$, $-(CH_2)_{0-2}-(piperazinyl)$, $-(CH_2)_{0-2}-(piperidinyl)$, or $-(CH_2)_{0-2}-(morpholinyl)$; wherein the phenyl group at each occurrence is optionally substituted with 1 or 2 groups that are independently R_{205} or R_{210} ; wherein each heterocycloalkyl group at each occurrence is optionally substituted with 1 or 2 R_{210} ; wherein each heteroaryl group at each occurrence is optionally substituted with 1 or 2 R_{210} ;

R₂₂₀ and R₂₂₅ at each occurrence are independently -H, -C₁-C₄ alkyl, hydroxy C₁-C₄ alkyl, halo C₁-C₄ alkyl; -C₃-C₆ cycloalkyl, or -(C₁-C₄ alkyl)-O-(C₁-C₂ alkyl);

5 R₂₃₅ and R₂₄₀ at each occurrence are independently H, or C₁-C₆ alkyl;

R₂₄₅ and R₂₅₀ at each occurrence are independently H, C₁-C₄ alkyl, C₁-C₄ hydroxyalkyl, C₁-C₄ alkoxy, or C₁-C₄ haloalkoxy, or

10 R₂₄₅ and R₂₅₀ are taken together with the carbon to which they are attached to form a carbocycle of 3, 5, or 6 carbon atoms.

Even more preferred compounds of formula X-VII include those wherein:

15 R₅₁ is benzyl; phenethyl; C₁-C₆ alkyl optionally substituted with 1, 2, or 3 groups that are independently halogen, cyano, -NR₆R₇, -C(O)NR₆R₇, or -C₁-C₄ alkoxy; pyrrolidinyl, tetrahydrofuryl, tetrahydro-thienyl 1,1-dioxide, tetrahydrothienyl, pyranyl, piperidinyl, pyrrolidinonyl, 20 dihydropyridazinonyl, 2-thioxo-thiazolidin-4-one, each of which is optionally substituted with 1 or 2 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, C₂-C₄ alkanoyl, benzyl, and -SO₂ C₁-C₄ alkyl; pyrrolidinonyl C₁-C₄ alkyl optionally substituted with 1 or 2 groups that 25 are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, C₂-C₄ alkanoyl, phenyl C₁-C₄ alkyl, and -SO₂ C₁-C₄ alkyl; C₂-C₄ alkenyl; C₂-C₄ alkynyl; pyrazolyl, imidazolyl, pyrazinyl, pyridyl, isoxazolyl, thiazolyl, indolyl, each of which is optionally substituted with 1, 2, or 3 groups that are 30 independently OH, C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, NH₂, NH(C₁-C₆ alkyl) or N(C₁-C₆ alkyl)(C₁-C₆ alkyl); pyridinyl C₁-C₄ alkyl optionally substituted with 1, 2, or 3 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, NH₂, NH(C₁-C₆ alkyl) or N(C₁-C₆ alkyl)(C₁-C₆ alkyl); phenyl;

cyclopropyl; cyclopentyl; cyclohexyl; cyclopropylmethyl;
wherein the phenyl; cycloalkyl, and cycloalkylalkyl groups
are optionally substituted with 1, 2, or 3 groups that are
independently halogen, CN, NO₂, C₁-C₄ alkyl, C₁-C₄ alkoxy,
5 C₂-C₆ alkanoyl, C₁-C₄ haloalkyl, C₁-C₄ haloalkoxy, hydroxy,
C₁-C₄ hydroxyalkyl, or C₁-C₄ thioalkoxy;

R₆ and R₇ are independently H, C₁-C₄ alkyl, C₂-C₄ alkanoyl,
or benzyl;

X is-C₁-C₃ alkylidenyl optionally optionally substituted with 1
10 or 2 methyl groups;

Z is SO₂; SO; S; or C(O);

Y is C₁-C₄ haloalkyl; OH; -N(Y₁)(Y₂); C₁-C₁₀ alkyl optionally
substituted with 1 or 2 substituents which can be the same
or different and are selected from the group consisting of
15 halogen, hydroxy, C₁-C₄ alkoxy, C₁-C₄ thioalkoxy, and C₁-C₄
haloalkoxy; C₁-C₄ alkoxy; phenyl optionally substituted
with halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, CN or NO₂; or
benzyl optionally substituted with halogen, C₁-C₄ alkyl,
C₁-C₄ alkoxy, CN or NO₂; wherein

20 Y₁ and Y₂ are the same or different and are H; C₁-C₆ alkyl
optionally substituted with 1, 2, or 3 substituents
selected from halogen, C₁-C₂ alkoxy, C₃-C₆ cycloalkyl,
and OH; C₂-C₆ alkanoyl; phenyl; -SO₂-C₁-C₄ alkyl;
benzyl; and C₃-C₆ cycloalkyl C₁-C₂ alkyl; or

25 -N(Y₁)(Y₂) forms a ring selected from piperazinyl,
piperidinyl, morpholinyl, and pyrrolidinyl, wherein
each ring is optionally substituted with 1, 2, 3, or
4 groups that are independently C₁-C₆ alkyl, C₁-C₆
alkoxy, C₁-C₆ alkoxy C₁-C₆ alkyl, or halogen.

30 Other even more preferred compounds of formula X-VII
include those wherein:

X is-C₁-C₃ alkylidenyl;

Z is SO₂; SO; S; or C(O);

Y is OH; -N(Y₁)(Y₂); phenyl; benzyl; or C₁-C₁₀ alkyl optionally substituted with 1 or 2 substituents which can be the same or different and are selected from halogen, hydroxy, methoxy, ethoxy, thiomethoxy, thioethoxy, and CF₃; wherein
5 Y₁ and Y₂ are the same or different and are H; C₁-C₄ alkyl optionally substituted with 1 or 2 substituents selected from halogen, methoxy, ethoxy, cyclopropyl, and OH; or

-N(Y₁)(Y₂) forms a ring selected from piperazinyl,
10 piperidinyl, morpholinyl, and pyrrolidinyl, wherein each ring is optionally substituted with 1 or 2 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, or halogen;

R₁ is benzyl which is optionally substituted with 1, 2, or 3
15 groups independently selected from methyl, ethyl, n-propyl, isopropyl, hydroxymethyl, monohalomethyl, dihalomethyl, trihalomethyl, -CH₂CF₃, methoxymethyl, halogen, methoxy, ethoxy, n-propyloxy, isopropyloxy, and OH;

20 R₂ and R₃ are independently H or C₁-C₄ alkyl,
R₂₀ at each occurrence is independently hydrogen, C₁-C₄ alkyl, or C₂-C₄ alkanoyl;

R_C is C₁-C₆ alkyl optionally substituted with 1, 2, or 3 R₂₀₅
groups; cyclopropyl, cyclopropylmethyl, cyclopentyl,
25 cyclopentylmethyl, cyclohexyl, cyclohexylmethyl;
-(CR₂₄₅R₂₅₀)₀₋₃-phenyl optionally substituted with 1 or 2 R₂₀₀ groups; or -(CR₂₄₅R₂₅₀)₀₋₃-pyridyl optionally substituted with 1 or 2 R₂₀₀;

R₂₀₀ at each occurrence is independently C₁-C₄ alkyl
30 optionally substituted with 1 or 2 R₂₀₅ groups; OH; or halogen;

R₂₀₅ at each occurrence is independently C₁-C₄ alkyl, halogen, -OH, -SH, -C≡N, -CF₃, or C₁-C₄ alkoxy;

R₂₄₅ and R₂₅₀ at each occurrence are independently H, C₁-C₄ hydroxyalkyl, or C₁-C₄ alkoxy, or

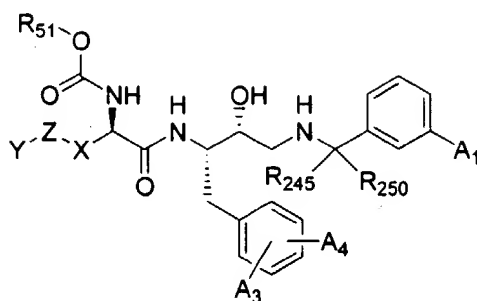
R₂₄₅ and R₂₅₀ are taken together with the carbon to which they are attached to form a carbocycle of 3 carbon atoms.

Additional more preferred compounds of formula X-VII include those wherein:

R₅₁ is benzyl; phenethyl; C₁-C₆ alkyl optionally substituted with 1, 2, or 3 groups that are independently halogen, cyano, -NR₆R₇, -C(O)NR₆R₇, or -C₁-C₄ alkoxy; pyrrolidinyl, tetrahydrofuryl, tetrahydro-thienyl 1,1-dioxide, tetrahydrothienyl, pyranyl, piperidinyl, pyrrolidinonyl, each of which is optionally substituted with 1 or 2 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, C₂-C₄ alkanoyl, benzyl, and -SO₂ C₁-C₄ alkyl; pyrrolidinonyl C₁-C₄ alkyl optionally substituted with 1 or 2 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, C₂-C₄ alkanoyl, C₁-C₄ alkyl, and -SO₂ C₁-C₄ alkyl; C₂-C₄ alkenyl; C₂-C₄ alkynyl; pyridinyl C₁-C₄ alkyl optionally substituted with 1, or 2 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, NH₂, NH(C₁-C₆ alkyl) or N(C₁-C₆ alkyl)(C₁-C₆ alkyl); cyclopentyl; cyclohexyl; or cyclopropylmethyl; wherein the cycloalkyl, and cycloalkylalkyl groups are optionally substituted with 1, or 2 groups that are independently halogen, CN, NO₂, methyl, ethyl, methoxy, ethoxy, C₂-C₄ alkanoyl, CF₃, OCF₃, or hydroxy;

R₆ and R₇ are independently H, C₁-C₄ alkyl, C₂-C₄ alkanoyl, or benzyl;

Y is OH; -N(Y₁)(Y₂); phenyl; benzyl; or C₁-C₁₀ alkyl optionally substituted with 1 or 2 substituents which can be the same or different and are selected from halogen, hydroxy, methoxy, ethoxy, thiomethoxy, thioethoxy, and CF₃; wherein



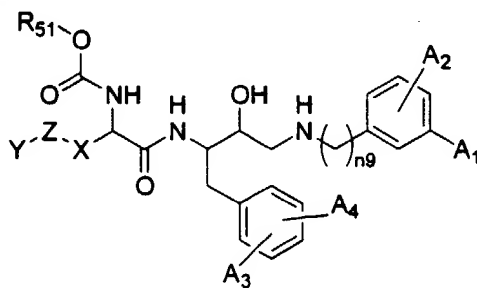
X-VIII-a

wherein

A₃ and A₄ are independently H, F, Cl, methyl or methoxy; and

- 5 R₅₁ is benzyl; phenethyl; CH₃; CH₂CF₃; CH₂CH₂CN; CH₂CH₂NHC(O)CH₃; CH₂C(O)N(CH₂CH₃)₂; isopropyl; CH₂CH₂OCH₃; pyrrolidinyl, tetrahydrofuryl, tetrahydro-thienyl 1,1-dioxide, tetrahydrothienyl, pyranyl, piperidinyl, pyrrolidinonyl, each of which is optionally substituted with 1 or 2 groups
- 10 that are independently methyl, ethyl, methoxy, ethoxy, halogen, C₂-C₄ alkanoyl, benzyl, and -SO₂ C₁-C₄ alkyl; pyrrolidinonyl C₁-C₄ alkyl; allyl; propargyl; pyridinyl C₁-C₄ alkyl; cyclopentyl; cyclohexyl; or cyclopropylmethyl.

- 15 Other preferred compounds of formula X-VII include those of formula X-IX



X-IX

wherein

- 20 n₉ is 1 or 2;
- A₁ and A₂ are independently H, methyl, ethyl, propyl, methoxy, F, Cl, Br, I, CF₃ or C₂-C₆ alkynyl; and
- A₃ and A₄ are independently F, Cl, Br, I, methyl, methoxy, or H.

Preferred compounds of formula X-IX include those wherein
A₁ is methyl, ethyl, I, or C₂ alkynyl;

A₃ and A₄ are independently H, F, Cl, Br, or I;

5 X is C₁ or C₂ alkylidenyl;

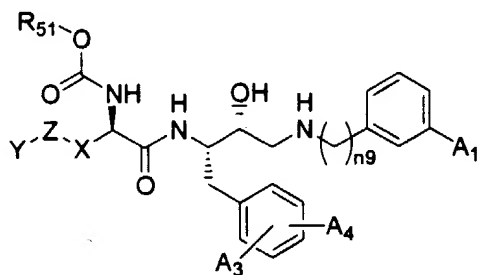
Z is SO₂; SO; S; or C(O); and

Y is phenyl, methyl, propyl, n-butyl, isobutyl, isopentyl, 4-heptyl, 3-heptyl, 3-pentyl, or 5-nonyl; or

Y is -N(Y₁)(Y₂); wherein

10 Y₁ and Y₂ are independently H or C₁-C₄ alkyl.

More preferred compounds of formula X-IX include those of
formula X-IX-a



X-IX-a

15 wherein

A₃ and A₄ are both H or both F; and

R₅₁ is benzyl; phenethyl; CH₃; CH₂CF₃; CH₂CH₂CN; CH₂CH₂NHC(O)CH₃;
CH₂C(O)N(CH₂CH₃)₂; isopropyl; CH₂CH₂OCH₃; pyrrolidinyl;

20 tetrahydrofuryl; tetrahydro-thienyl 1,1-dioxide;

tetrahydrothienyl; pyranyl; piperidinyl; pyrrolidinonyl;

each of which is optionally substituted with 1 or 2 groups
that are independently methyl, ethyl, methoxy, ethoxy,

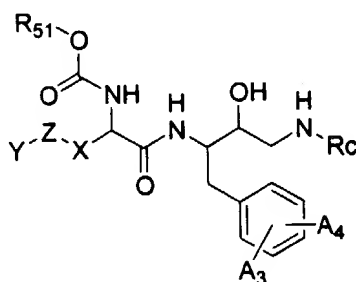
halogen, C₂-C₄ alkanoyl, benzyl, and -SO₂ C₁-C₄ alkyl;

25 pyrrolidinonyl C₁-C₄ alkyl; allyl; propargyl; pyridinyl C₁-
C₄ alkyl; cyclopentyl; cyclohexyl; or -(C₁-C₄)alkyl-
cyclopropyl.

Preferred compounds of formula X-VII include those of formula X-X, i.e. compounds of formula X-VII wherein R_C is C_3 - C_8 alkyl, cyclopropyl, cyclopentyl, cyclohexyl, or -
(C_1 - C_4)alkyl-cyclopropyl.

5

Preferred compounds of formula X-X include those of formula X-X-a:



X-X-a

10 wherein

A₃ and A₄ are independently F, Cl, Br, I, methyl, ethyl, methoxy, ethoxy, or H;

X is C₁ or C₂ alkylidenyl;

Z is SO₂; SO; S; or C(O); and

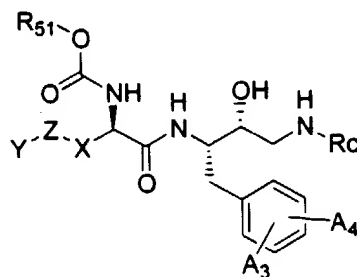
15 Y is phenyl, C₁-C₁₀ alkyl. More preferably, Y is methyl, propyl, n-butyl, isobutyl, isopentyl, 4-heptyl, 3-heptyl, 3-pentyl, or 5-nonyl. Or,

Y is -N(Y₁)(Y₂); wherein

Y₁ and Y₂ are independently H or C₁-C₄ alkyl.

20

More preferred compounds of formula X-X include those of formula X-X-b:



X-X-b

wherein

A₃ and A₄ are independently H, F, Cl, methyl, ethyl, methoxy, ethoxy, CF₃ or OCF₃; and

R₅₁ is benzyl; phenethyl; CH₃; CH₂CF₃; -CH₂CH₂CN; CH₂CH₂NHC(O)CH₃;

5 -CH₂C(O)N(CH₂CH₃)₂; isopropyl; CH₂CH₂OCH₃; pyrrolidinyl, tetrahydrofuryl, tetrahydro-thienyl 1,1-dioxide, tetrahydrothienyl, pyranyl, piperidinyl, pyrrolidinonyl, each of which is optionally substituted with 1 or 2 groups that are independently methyl, ethyl, methoxy, ethoxy,
10 halogen, C₂-C₄ alkanoyl, benzyl, and -SO₂ C₁-C₄ alkyl; pyrrolidinonyl C₁-C₄ alkyl; allyl; propargyl; pyridinyl C₁-C₄ alkyl; cyclopentyl; cyclohexyl; or cyclopropylmethyl.

Representative compounds of formula X-VII are

3-(butylsulfinyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(methoxy)carbonyl]-D-alaninamide;

S-butyl-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(methoxy)carbonyl]-D-cysteinamide;

N~2~-[(benzyloxy)carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(4,4,4-trifluorobutyl)sulfonyl]-D-alaninamide;

N~2~-[(benzyloxy)carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(4,4,4-trifluorobutyl)sulfinyl]-D-alaninamide;

N~2~-[(benzyloxy)carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-S-(4,4,4-trifluorobutyl)-D-cysteinamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(methoxy)carbonyl]-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(2,2,2-

trifluoroethoxy) carbonyl]-D-alaninamide;

N~2~-[(2-cyanoethoxy) carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-(butylsulfonyl)-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-{[(3R)-pyrrolidin-3-yl] carbonyl}-D,L-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-{[(3S)-tetrahydrofuran-3-yloxy] carbonyl}-D-alaninamide;

N~2~-{[2-(acetylamino) ethoxy] carbonyl}-3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-{[(pyridin-3-yl)methyl]oxy] carbonyl}-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-{[(pyridin-4-yl)methyl]oxy] carbonyl}-D-alaninamide;

3-(butylsulfonyl)-N~2~-[(methoxy) carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-(cyclopropylamino)-2-hydroxypropyl}-D-alaninamide;

3-(butylsulfonyl)-N~2~-[(2-cyanoethoxy) carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-(cyclopropylamino)-2-hydroxypropyl}-D-alaninamide;

N~2~-[(benzyloxy) carbonyl]-3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-methylbutyl) amino]-2-hydroxypropyl}-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-methylbutyl) amino]-2-hydroxypropyl}-N~2~-[(methyloxy) carbonyl]-D-alaninamide;

N~2~-[(2-cyanoethoxy) carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-(cyclopropylamino)-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~2~-([2-(acetylamino)ethoxy]carbonyl)-N~1~-((1S,2R)-1-(3,5-difluorobenzyl)-3-(cyclopropylamino)-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~1~-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-methylbutyl)amino]-2-hydroxypropyl)-N~2~-[(methyloxy)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~2~-[(benzyloxy)carbonyl]-N~1~-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-methylbutyl)amino]-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~2~-([2-(diethylamino)-2-oxoethoxy]carbonyl)-N~1~-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~1~-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N~2~-[(methoxy)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~1~-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N~2~-[(isopropoxy)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~2~-[(cyclopropylmethoxy)carbonyl]-N~1~-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~2~-[(allyloxy)carbonyl]-N~1~-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~2~-[(2-cyanoethoxy)carbonyl]-N~1~-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~2~-([2-(acetylamino)ethoxy]carbonyl)-N~1~-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~1~-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]-N~2~-[[[pyridin-3-

yl)methyl]oxy]carbonyl}-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]-N~2~-{[(pyridin-4-yl)methyl]oxy]carbonyl}-D-alaninamide;

benzyl (1R)-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)amino)carbonyl]-3-(methylsulfonyl)propylcarbamate;

N~2~-[(benzyloxy)carbonyl]-3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-D-alaninamide trifluoroacetate;

N~2~-[(benzyloxy)carbonyl]-3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-L-alaninamide trifluoroacetate;

N~2~-[(benzyloxy)carbonyl]-N~1~-{(1S,2S)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1R)-2-hydroxy-1-phenylethyl]amino)propyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~2~-[(benzyloxy)carbonyl]-N~1~-{(1S,2S)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1R)-2-methoxy-1-phenylethyl]amino)propyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~2~-[(benzyloxy)carbonyl]-N~1~-{(1S,2S)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1S)-2-methoxy-1-phenylethyl]amino)propyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~2~-[(benzyloxy)carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethylphenyl)cyclopropyl]amino]-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]-N~2~-[(prop-2-ynyl)oxy]carbonyl}-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-

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ethylbenzyl) amino]-2-hydroxypropyl}-N-2--(2-methoxyethylcarbonyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N-2--{[(3R)-1-acetylpyrrolidin-3-yl]carbonyl}-N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N-2--{[(3S)-tetrahydrofuran-3-yloxy]carbonyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N-2--{[(3S)-tetrahydrofuran-3-yloxy]carbonyl}-3-[(1-propylbutyl)sulfonyl]-L-alaninamide;

N-2--[(benzyloxy)carbonyl]-N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N-2--[(benzyloxy)carbonyl]-N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-L-alaninamide;

N-2--[(benzyloxy)carbonyl]-N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethylphenyl)cyclopropyl] amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N-2--[(benzyloxy)carbonyl]-N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N-2--[(benzyloxy)carbonyl]-N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-methylbutyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N-2--[(benzyloxy)carbonyl]-N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-(cyclopropylamino)-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N-2--[(benzyloxy)carbonyl]-N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(cyclopropylmethyl) amino]-2-hydroxypropyl}-

3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;
N~2~-[(benzyloxy)carbonyl]-N~1~-{(1S,2S)-1-(3,5-difluorobenzyl)-3-[(3-ethylphenyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;
N~2~-[(benzyloxy)carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(2-[3-(trifluoromethyl)phenyl]ethyl)amino]propyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;
N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-N~2~-{[(pyridin-3-yl)methyl]oxy}carbonyl}-D,L-alaninamide;
N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-{[(3S)-tetrahydrofuran-3-yloxy]carbonyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;
N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-{[(3R)-tetrahydrofuran-3-yloxy]carbonyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;
N~1~-{(1S,2R)-1-benzyl-3-[(3-methoxybenzyl)amino]-2-hydroxypropyl}-N~2~-{[(3S)-tetrahydrofuran-3-yloxy]carbonyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;
N~2~-{[(3R)-1-acetylpyrrolidin-3-yl]carbonyl}-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;
N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-N~2~-{[(3R)-pyrrolidin-3-yl]carbonyl}-D,L-alaninamide;
N~2~-{[(3R)-1-benzylpyrrolidin-3-yl]carbonyl}-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;
N~1~-{(1S,2R)-1-(3,5difluorobenzyl)-3-[(3-

ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-{[(3S)-1,1-dioxidotetrahydrothien-3-yloxy]carbonyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-{[(3S)-tetrahydrothiophen-3-yloxy]carbonyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~2~-{(cyclopentylcarbonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~2~-{(cyclohexylcarbonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-3-(cyclopropylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-N~2~-{[tetrahydropyran-4-yloxy]carbonyl}-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-N~2~-{[tetrahydropyran-4-yloxy]carbonyl}-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-{[1-(methylsulfonyl)piperidin-4-yloxy]carbonyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~2~-{[1-acetylpiperidin-4-yloxy]carbonyl}-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-{[[[(3S)-5-oxopyrrolidin-3-yl]methyl]oxy]carbonyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N~2~-{[[[(3R)-5-oxopyrrolidin-3-yl]methyl]oxy]carbonyl}-3-[(1-

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propylbutyl) sulfonyl]-D,L-alaninamide;

N~1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2--{[2-methoxyethyl]oxy]carbonyl}-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N~2--[(benzyloxy)carbonyl]-3-(butylsulfonyl)-N~1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-D,L-alaninamide;

N~1--{(1S,2R)-1-benzyl-3-[(3-methoxybenzyl)amino]-2-hydroxypropyl}-N~2--[(benzyloxy)carbonyl]-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N~2--[(benzyloxy)carbonyl]-N~1--{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[2-(3-methoxyphenyl)ethyl]amino]propyl}-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N~2--[(benzyloxy)carbonyl]-N~1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~5~,N~5--dipropyl-L-glutamamide;

N~2--[(benzyloxy)carbonyl]-N~1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~5~,N~5--dipropyl-D-glutamamide;

methyl (1R)-1-[[{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]amino]carbonyl]-3-oxoheptylcarbamate;

4-butyl-N~1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2--(methoxycarbonyl)-D-homoserinamide;

3-(2-butyl-1,3-dioxolan-2-yl)-N~1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2--(methoxycarbonyl)-D-alaninamide;

3-(2-butyl-1,3-dioxan-2-yl)-N~1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2--(methoxycarbonyl)-D-alaninamide;

methyl (1R)-1-[[{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-

ethylbenzyl)amino]-2-hydroxypropyl)amino)carbonyl]-3,3-difluoroheptylcarbamate;

methyl (1R)-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)amino)carbonyl]-3-fluoroheptylcarbamate;

methyl (1R)-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)amino)carbonyl]-4-oxooctylcarbamate;

methyl (1R)-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)amino)carbonyl]-4-hydroxyoctylcarbamate;

methyl (1R)-3-(2-butyl-1,3-dioxolan-2-yl)-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)amino)carbonyl]propylcarbamate;

methyl (1R)-3-(2-butyl-1,3-dioxan-2-yl)-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)amino)carbonyl]propylcarbamate;

methyl (1R)-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)amino)carbonyl]-4-fluorooctylcarbamate;

methyl (1R)-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)amino)carbonyl]-4,4-difluorooctylcarbamate;

3-(butylsulfonyl)-N-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethynylbenzyl)amino]-2-hydroxypropyl)-N-2-(methoxycarbonyl)-D-alaninamide;

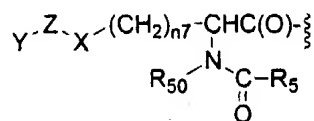
3-(butylsulfonyl)-N-1-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[3-(trifluoromethyl)benzyl]amino]propyl)-N-2-(methoxycarbonyl)-D-alaninamide;

3-(butylsulfonyl)-N-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethylphenyl)cyclopropyl]amino]-2-hydroxypropyl)-N-2-(methoxycarbonyl)-D-alaninamide;

3-(butylsulfonyl)-N-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethynylphenyl)cyclopropyl]amino]-2-hydroxypropyl)-

3-(butylsulfonyl)-N-1-~[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-({1-[3-(trifluoromethyl)phenyl]cyclopropyl}amino)propyl]-N-2-(methoxycarbonyl)-D-alaninamide; and pharmaceutically acceptable salts thereof.

R_N is:



R₅ is selected from the group consisting of cyclopropyl;

cyclopentyl; cyclohexyl; C₁-C₆ alkyl optionally substituted with 1, 2, or 3 groups that are independently halogen, -NR₆R₇, C₁-C₄ alkoxy, C₅-C₆ heterocycloalkyl, C₅-C₆ heteroaryl, phenyl, C₃-C₇ cycloalkyl, -S-C₁-C₄ alkyl, -SO₂-C₁-C₄ alkyl, -CO₂H, -CONR₆R₇, -CO₂-C₁-C₄ alkyl, or phenyloxy; heteroaryl optionally substituted with 1, 2, or 3 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, C₁-C₄ haloalkyl, or OH; heterocycloalkyl optionally substituted with 1, 2, or 3 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, or C₂-C₄ alkanoyl; phenyl optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, OH, C₁-C₄ alkyl, C₁-C₄ alkoxy, or C₁-C₄ haloalkyl; and -NR₆R₇; wherein R₆ and R₇ are independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkanoyl, phenyl, -SO₂-C₁-C₄ alkyl, and phenyl C₁-C₄ alkyl;

X is C₁-C₄ alkylidenyl optionally optionally substituted with
1, 2, or 3 methyl groups; or -NR₄₋₆-; or

R₄ and R₄₋₆ combine to form -(CH₂)_{n10}-, wherein
n₁₀ is 1, 2, 3, or 4;

5 Z is a bond; SO₂; SO; S; or C(O);

Y is H; C₁-C₄ haloalkyl; C₅-C₆ heterocycloalkyl containing at
least one N, O, or S; phenyl; OH; -N(Y₁)(Y₂); C₁-C₁₀ alkyl
optionally substituted with 1 thru 3 substituents which
can be the same or different and are selected from
10 halogen, hydroxy, alkoxy, thioalkoxy, and haloalkoxy; C₃-
C₈ cycloalkyl optionally substituted with 1, 2, or 3
groups independently selected from C₁-C₃ alkyl, and
halogen; alkoxy; phenyl optionally substituted with
halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, CN or NO₂; or phenyl C₁-
15 C₄ alkyl optionally substituted with halogen, C₁-C₄ alkyl,
C₁-C₄ alkoxy, CN or NO₂; wherein

Y₁ and Y₂ are the same or different and are H; C₁-C₁₀ alkyl
optionally substituted with 1, 2, or 3 substituents
selected from halogen, C₁-C₄ alkoxy, C₃-C₈ cycloalkyl,
20 and OH; C₂-C₆ alkenyl; C₂-C₆ alkanoyl; phenyl; -SO₂-C₁-
C₄ alkyl; phenyl C₁-C₄ alkyl; or C₃-C₈ cycloalkyl C₁-C₄
alkyl; or

-N(Y₁)(Y₂) forms a ring selected from piperazinyl,
piperidinyl, morpholinyl, and pyrrolidinyl, wherein
25 each ring is optionally substituted with 1, 2, 3, or
4 groups that are independently C₁-C₆ alkyl, C₁-C₆
alkoxy, C₁-C₆ alkoxy C₁-C₆ alkyl, or halogen; and

R₂₀ at each occurrence is independently hydrogen, C₁-C₆ alkyl,
C₁-C₆ alkoxy C₁-C₆ alkyl, halo C₁-C₆ alkyl, or C₁-C₆
30 alkanoyl, each of which is unsubstituted or substituted
with 1, or 2 groups independently selected from halogen,
C₁-C₆ alkyl, hydroxy, C₁-C₆ alkoxy, NH₂, and -R₂₆-R₂₇,
wherein

R₂₆ is -C(O)-, -SO₂-, -CO₂-, -C(O)NH-, or -C(O)N(C₁-C₆ alkyl)-;

R₂₇ is C₁-C₆ alkyl, C₁-C₆ alkoxy, aryl C₁-C₆ alkyl, heterocycloalkyl, or heteroaryl, wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, halo C₁-C₆ alkyl, hydroxy C₁-C₆ alkyl, -C(O)NH₂, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)(C₁-C₆ alkyl), -C(O)NH(C₁-C₆ alkyl), or -C(O)N(C₁-C₆ alkyl)(C₁-C₆ alkyl).

Preferred compounds of formula X-XI include those of formula X-XI-a, i.e., formula X-XI wherein

R₂ and R₃ are independently H or C₁-C₆ alkyl optionally substituted with 1, or 2 substituents selected from halogen, OH, SH, C≡N, CF₃, and C₁-C₃ alkoxy; and

R_C is C₁-C₈ alkyl optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of R₂₀₅, -OC=ONR₂₃₅R₂₄₀, -S(=O)₀₋₂(C₁-C₆ alkyl), -SH, -C=ONR₂₃₅R₂₄₀, and -S(=O)₂NR₂₃₅R₂₄₀; -(CH₂)₀₋₃-(C₃-C₈) cycloalkyl wherein the cycloalkyl is optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of R₂₀₅, -CO₂H, and -CO₂-(C₁-C₄ alkyl); -(CR₂₄₅R₂₅₀)₀₋₄-phenyl; -(CR₂₄₅R₂₅₀)₀₋₄-heteroaryl; -(CR₂₄₅R₂₅₀)₀₋₄-heterocycloalkyl; or -(CH₂)₀₋₁-CH(C₁-C₄ hydroxyalkyl)-(CH₂)₀₋₁-heteroaryl; wherein each aryl is optionally substituted with 1, 2, or 3 R₂₀₀; each heteroaryl is optionally substituted with 1, 2, 3, or

4 R₂₀₀;

each heterocycloalkyl is optionally substituted with 1, 2, 3, or 4 R₂₁₀;

R₂₀₀ at each occurrence is independently C₁-C₆ alkyl optionally substituted with 1, 2, or 3 R₂₀₅ groups; OH; -NO₂; halogen; -CO₂H; C≡N; -(CH₂)₀₋₄-CO-NR₂₂₀R₂₂₅; -(CH₂)₀₋₄-CO-(C₁-C₁₂ alkyl); -(CH₂)₀₋₄-CO₂R₂₁₅; or -(CH₂)₀₋

$4-O-(C_1-C_6 \text{ alkyl optionally substituted with 1, 2, 3, or 5 -F})$;

R_{205} at each occurrence is independently C_1-C_6 alkyl, halogen, $-OH$, $-O\text{-phenyl}$, $-SH$, $-C\equiv N$, $-CF_3$, C_1-C_6 alkoxy, NH_2 , $NH(C_1-C_6 \text{ alkyl})$, or $N-(C_1-C_6 \text{ alkyl})(C_1-C_6 \text{ alkyl})$;

R_{210} at each occurrence is independently C_1-C_6 alkyl optionally substituted with 1, 2, or 3 R_{205} groups; halogen; C_1-C_6 alkoxy; C_1-C_6 haloalkoxy; $-NR_{220}R_{225}$; OH ; $C\equiv N$; C_3-C_7 cycloalkyl optionally substituted with 1, 2, or 3 R_{205} groups; $-CO-(C_1-C_4 \text{ alkyl})$; $-SO_2-NR_{235}R_{240}$; $-CO-NR_{235}R_{240}$; $-SO_2-(C_1-C_4 \text{ alkyl})$; or $=O$; wherein

R_{215} at each occurrence is independently C_1-C_6 alkyl, $-(CH_2)_{0-2}\text{-(phenyl)}$, C_3-C_7 cycloalkyl, and $-(CH_2)_{0-2}\text{-(heteroaryl)}$, or $-(CH_2)_{0-2}\text{-(heterocycloalkyl)}$; wherein the phenyl group at each occurrence is optionally substituted with 1, 2, or 3 groups that are independently R_{205} or R_{210} ; wherein the heterocycloalkyl group at each occurrence is optionally substituted with 1, 2, or 3 R_{210} ; wherein each heteroaryl group at each occurrence is optionally substituted with 1, 2, or 3 R_{210} ;

R_{220} and R_{225} at each occurrence are independently $-H$, $-C_1-C_6$ alkyl, hydroxy C_1-C_4 alkyl, halo C_1-C_4 alkyl; $-C_3-C_7$ cycloalkyl, or $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_3 \text{ alkyl})$;

R_{235} and R_{240} at each occurrence are independently H , or C_1-C_6 alkyl;

R_{245} and R_{250} at each occurrence are independently H , C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 alkoxy, or C_1-C_4 haloalkoxy, or

R_{245} and R_{250} are taken together with the carbon to which they are attached to form a carbocycle of 3, 4, 5, or 6 carbon atoms.

More preferred compounds of formula X-XI-a include those of formula X-XI-b, i.e. X-XI-a, wherein

R₁ is benzyl which is optionally substituted with 1, 2, 3, or 4 groups independently selected from C₁-C₄ alkyl optionally substituted with 1, or 2 substituents selected from halogen, -OH, -SH, NH₂, NH(C₁-C₆ alkyl), N-(C₁-C₆ alkyl)(C₁-C₆ alkyl), -C≡N, -CF₃, and C₁-C₃ alkoxy; halogen; C₁-C₄ alkoxy; and OH.

Even more preferred compounds of formula X-XI-b include those of formula X-XI-c, i.e., X-XI-b wherein

n₇ is 0, 1, or 2;

R₅ is selected from the group consisting of cyclopropyl;

cyclopentyl; cyclohexyl; C₁-C₆ alkyl optionally substituted with 1, 2, or 3 groups that are independently halogen, -NR₆R₇, C₁-C₄ alkoxy, C₅-C₆ heterocycloalkyl, C₅-C₆ heteroaryl, phenyl, C₃-C₇ cycloalkyl, -S-C₁-C₄ alkyl, -SO₂-C₁-C₄ alkyl, -CO₂H, -CONR₆R₇, -CO₂-C₁-C₄ alkyl, or phenyloxy; pyridyl, thiazolyl, pyrazolyl, pyrazinyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, C₁-C₄ haloalkyl, or OH; piperidinyl, dihydropyridazinonyl, pyrrolidinonyl, thioxothiazolidinonyl, isoxazolyl, imidazolyl, indolyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, or C₂-C₄ alkanoyl; phenyl optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, OH, C₁-C₄ alkyl, C₁-C₄ alkoxy, or C₁-C₄ haloalkyl; and -NR₆R₇; wherein

R₆ and R₇ are independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkanoyl, phenyl, -SO₂-C₁-C₄ alkyl, benzyl, and phenethyl.

More preferred compounds of formulae X-XI, X-XI-a, X-XI-b and X-XI-c include those wherein

R₂₀ at each occurrence is independently hydrogen, C₁-C₆ alkyl, C₁-C₂ alkoxy C₁-C₄ alkyl, C₂-C₆ alkanoyl, each of which is
5 unsubstituted or substituted with 1 or 2 groups independently selected from halogen, hydroxy, C₁-C₄ alkoxy, tertiary-butoxy carbonyl, benzyloxycarbonyl, and NH₂;

R_c is C₁-C₈ alkyl optionally substituted with 1, 2, or 3 groups
10 independently selected from the group consisting of R₂₀₅, -SH, -C=ONR₂₃₅R₂₄₀, and -S(=O)₂NR₂₃₅R₂₄₀; -(CH₂)₀₋₃-(C₃-C₆) cycloalkyl wherein the cycloalkyl is optionally substituted with 1, 2, or 3 groups independently selected
15 from the group consisting of R₂₀₅, -CO₂H, and -CO₂-(C₁-C₄ alkyl); -(CR₂₄₅R₂₅₀)₀₋₄-phenyl optionally substituted with 1, 2, or 3 R₂₀₀; -(CR₂₄₅R₂₅₀)₀₋₃-pyridyl; -(CR₂₄₅R₂₅₀)₀₋₃-pyridazinyl; -(CR₂₄₅R₂₅₀)₀₋₃-pyrimidinyl; -(CR₂₄₅R₂₅₀)₀₋₃-pyrazinyl; -(CR₂₄₅R₂₅₀)₀₋₃-furyl; -(CR₂₄₅R₂₅₀)₀₋₃-indolyl;
20 -(CR₂₄₅R₂₅₀)₀₋₃-thienyl; -(CR₂₄₅R₂₅₀)₀₋₃-pyrrolyl; -(CR₂₄₅R₂₅₀)₀₋₃-pyrazolyl; (CR₂₄₅R₂₅₀)₀₋₃-benzoxazolyl; -(CR₂₄₅R₂₅₀)₀₋₃-imidazolyl; each of the above heteroaryl groups is optionally substituted with 1, 2, 3, or 4 R₂₀₀; -(CR₂₄₅R₂₅₀)₀₋₃-imidazolidinyl; (CR₂₄₅R₂₅₀)₀₋₃-tetrahydrofuryl; (CR₂₄₅R₂₅₀)₀₋₃-tetrahydropyranyl; (CR₂₄₅R₂₅₀)₀₋₃-piperazinyl; (CR₂₄₅R₂₅₀)₀₋₃-pyrrolidinyl; (CR₂₄₅R₂₅₀)₀₋₃-piperidinyl; (CR₂₄₅R₂₅₀)₀₋₃-indolinyl; each of the above heterocycloalkyl groups is
25 optionally substituted with 1, 2, 3, or 4 R₂₁₀; (CH₂)₀₋₁-CH((CH₂)₀₋₄-OH)-(CH₂)₀₋₁-phenyl; or -(CH₂)₀₋₁-CH(C₁-C₄ hydroxyalkyl)-(CH₂)₀₋₁-pyridyl;

30 R₂₀₀ at each occurrence is independently C₁-C₆ alkyl optionally substituted with 1, 2, or 3 R₂₀₅ groups; OH; -NO₂; halogen; -CO₂H; C≡N; -(CH₂)₀₋₄-CO-NR₂₂₀R₂₂₅; -(CH₂)₀₋₄-CO-(C₁-C₈ alkyl); -(CH₂)₀₋₄-CO₂R₂₁₅; or -(CH₂)₀₋

4-O-(C₁-C₆ alkyl optionally substituted with 1, 2, 3, or 5 -F);

R₂₀₅ at each occurrence is independently C₁-C₆ alkyl, halogen, -OH, -O-phenyl, -SH, -C≡N, -CF₃, C₁-C₆ alkoxy, NH₂, NH(C₁-C₆ alkyl), or N-(C₁-C₆ alkyl)(C₁-C₆ alkyl);

R₂₁₀ at each occurrence is independently C₁-C₆ alkyl optionally substituted with 1 or 2 R₂₀₅ groups; halogen; C₁-C₄ alkoxy; C₁-C₄ haloalkoxy; -NR₂₂₀R₂₂₅; OH; C≡N; C₃-C₇ cycloalkyl optionally substituted with 1 or 2 R₂₀₅ groups; -CO-(C₁-C₄ alkyl); -SO₂-NR₂₃₅R₂₄₀; -CO-NR₂₃₅R₂₄₀; -SO₂-(C₁-C₄ alkyl); or =O; wherein

R₂₁₅ at each occurrence is independently C₁-C₆ alkyl, -(CH₂)₀₋₂-(phenyl), C₃-C₆ cycloalkyl, -(CH₂)₀₋₂-(pyridyl), -(CH₂)₀₋₂-(pyrrolyl), -(CH₂)₀₋₂-(imidazolyl), -(CH₂)₀₋₂-(pyrimidyl), -(CH₂)₀₋₂-(pyrrolidinyl), -(CH₂)₀₋₂-(imidazolidinyl), -(CH₂)₀₋₂-(piperazinyl), -(CH₂)₀₋₂-(piperidinyl), or -(CH₂)₀₋₂-(morpholinyl); wherein the phenyl group at each occurrence is optionally substituted with 1 or 2 groups that are independently R₂₀₅ or R₂₁₀; wherein each heterocycloalkyl group at each occurrence is optionally substituted with 1 or 2 R₂₁₀; wherein each heteroaryl group at each occurrence is optionally substituted with 1 or 2 R₂₁₀;

R₂₂₀ and R₂₂₅ at each occurrence are independently -H, -C₁-C₄ alkyl, hydroxy C₁-C₄ alkyl, halo C₁-C₄ alkyl; -C₃-C₆ cycloalkyl, or -(C₁-C₄ alkyl)-O-(C₁-C₂ alkyl);

R₂₃₅ and R₂₄₀ at each occurrence are independently H, or C₁-C₆ alkyl;

R₂₄₅ and R₂₅₀ at each occurrence are independently H, C₁-C₄ alkyl, C₁-C₄ hydroxyalkyl, C₁-C₄ alkoxy, or C₁-C₄ haloalkoxy, or

R₂₄₅ and R₂₅₀ are taken together with the carbon to which they are attached to form a carbocycle of 3, 5, or 6 carbon atoms.

- 5 Still other more preferred compounds of formulae X-XI, X-XI-a, X-XI-b and X-XI-c include those wherein X is-C₁-C₃ alkylidenyl optionally optionally substituted with 1 or 2 methyl groups;
Z is SO₂; SO; S; or C(O);
10 Y is H; C₁-C₄ haloalkyl; pyrrolidinyl; piperidinyl; imidazolidinyl; piperazinyl; OH; -N(Y₁)(Y₂); C₁-C₁₀ alkyl optionally substituted with 1 thru 3 substituents which can be the same or different and are selected from halogen, hydroxy, C₁-C₄ alkoxy, C₁-C₄ thioalkoxy, and C₁-C₄ haloalkoxy;
15 C₃-C₆ cycloalkyl optionally substituted with 1, 2, or 3 groups independently selected from C₁-C₃ alkyl and halogen; C₁-C₄ alkoxy; phenyl, benzyl or phenethyl each of which is optionally substituted with halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, CN or NO₂; wherein
20 Y₁ and Y₂ are indepenently H; C₁-C₆ alkyl optionally substituted with 1, 2, or 3 substituents selected from halogen, C₁-C₄ alkoxy, C₃-C₆ cycloalkyl, and OH; C₂-C₆ alkanoyl; phenyl; -SO₂-C₁-C₄ alkyl; phenyl C₁-C₄ alkyl; or C₃-C₆ cycloalkyl C₁-C₄ alkyl; or
25 -N(Y₁)(Y₂) forms a ring selected from piperazinyl, piperidinyl, morpholinyl, and pyrrolidinyl, wherein each ring is optionally substituted with 1, 2, or 3 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ alkoxy C₁-C₄ alkyl, or halogen; and
30 R₂ and R₃ are independently H or C₁-C₄ alkyl.

Still other even more preferred compounds of formula X-XI include those of formula X-XII, i.e., compounds of formula X-XI wherein

n_7 is 0, or 1;

R_5 is selected from the group consisting of cyclopropyl;
cyclobutyl, cyclopentyl; cyclohexyl; C_1 - C_6 alkyl
optionally substituted with 1, 2, or 3 groups that are
independently halogen, $-NR_6R_7$, C_1 - C_4 alkoxy, piperidinyl,
pyrrolidinyl, tetrahydrofuryl, tetrahydrothienyl dioxide,
pyranyl, pyridyl, phenyl, C_3 - C_6 cycloalkyl, S - C_1 - C_4 alkyl,
 SO_2 - C_1 - C_4 alkyl, CO_2H , $CONR_6R_7$, CO_2 - C_1 - C_4 alkyl, or
phenyloxy; pyridyl, thiazolyl, pyrazolyl, pyrazinyl,
optionally substituted with 1, 2, or 3 groups that are
independently C_1 - C_4 alkyl, C_1 - C_4 alkoxy, halogen, C_1 - C_4
haloalkyl, or OH; piperidinyl, dihydropyridazinonyl,
pyrrolidinonyl, thioxothiazolidinonyl, isoxazolyl,
imidazolyl, indolyl, optionally substituted with 1, 2, or
3 groups that are independently C_1 - C_4 alkyl, C_1 - C_4 alkoxy,
halogen, or C_2 - C_4 alkanoyl; phenyl optionally substituted
with 1, 2, 3, or 4 groups that are independently halogen,
OH, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, or C_1 - C_2 haloalkyl; and
 $-NR_6R_7$; wherein

R_6 and R_7 are independently selected from the group
consisting of H, C_1 - C_4 alkyl, C_2 - C_6 alkanoyl, phenyl,
 $-SO_2$ - C_1 - C_4 alkyl, and benzyl;

R_{20} at each occurrence is independently hydrogen, C_1 - C_6 alkyl,
 C_2 - C_6 alkanoyl, tertiary-butoxy carbonyl, and
benzyloxycarbonyl;

R_C is C_1 - C_8 alkyl optionally substituted with 1 or 2 groups
independently selected from R_{205} , and $-SH$; $-(CH_2)_{0-3}$ - $(C_3$ - $C_6)$
cycloalkyl wherein the cycloalkyl is optionally
substituted with 1 R_{205} group; $-(CR_{245}R_{250})_{0-3}$ -phenyl
optionally substituted with 1 or 2 R_{200} ; $-(CR_{245}R_{250})_{0-3}$ -
pyridyl; $-(CR_{245}R_{250})_{0-3}$ -pyrrolyl; $(CR_{245}R_{250})_{0-3}$ -benzoxazolyl;
 $-(CR_{245}R_{250})_{0-3}$ -imidazolyl; each of the above heteroaryl
groups is optionally substituted with 1 or 2 R_{200} ; $-$
 $(CR_{245}R_{250})_{0-3}$ -imidazolidinyl; $(CR_{245}R_{250})_{0-3}$ -tetrahydrofuryl;

(CR₂₄₅R₂₅₀)₀₋₃-tetrahydropyranyl; (CR₂₄₅R₂₅₀)₀₋₃-pyrrolidinyl;
(CR₂₄₅R₂₅₀)₀₋₃-piperidinyl; each of the above
heterocycloalkyl groups is optionally substituted with 1
or 2 R₂₁₀; (CH₂)₀₋₁-CH((CH₂)₀₋₄-OH)-(CH₂)₀₋₁-phenyl; or -(CH₂)₀₋₁-CH(C₁-C₄ hydroxyalkyl)-(CH₂)₀₋₁-pyridyl;

R₂₀₀ at each occurrence is independently C₁-C₄ alkyl
optionally substituted with 1, 2, or 3 R₂₀₅ groups;
OH; NO₂; halogen; CO₂H; C≡N; or -(CH₂)₀₋₄-O-(C₁-C₆
alkyl optionally substituted with 1, 2, 3, or 5 -F);

R₂₀₅ at each occurrence is independently C₁-C₆ alkyl,
halogen, OH, -O-phenyl, SH, C≡N, CF₃, C₁-C₆ alkoxy,
NH₂, NH(C₁-C₆ alkyl), or N(C₁-C₆ alkyl)(C₁-C₆ alkyl);

R₂₁₀ at each occurrence is independently C₁-C₆ alkyl
optionally substituted with 1 R₂₀₅ group; halogen; C₁-

C₄ alkoxy; C₁-C₄ haloalkoxy; OH; C≡N; or =O; wherein
R₂₃₅ and R₂₄₀ at each occurrence are independently H, or C₁-
C₆ alkyl;

R₂₄₅ and R₂₅₀ at each occurrence are independently H, C₁-C₄
alkyl, C₁-C₄ hydroxyalkyl, C₁-C₄ alkoxy, or

R₂₄₅ and R₂₅₀ are taken together with the carbon to which
they are attached to form a carbocycle of 3, 5, or 6
carbon atoms;

X is-C₁-C₃ alkylidenyl;

Z is SO₂; SO; S; or C(O);

Y is H; C₁-C₄ haloalkyl; pyrrolidinyl; piperidinyl;

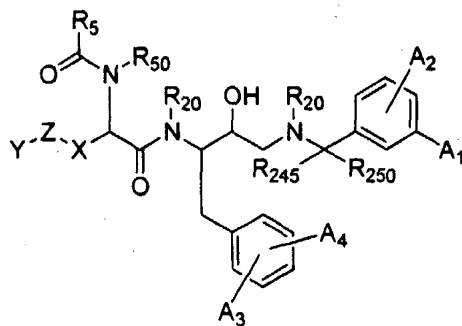
imidazolidinyl; piperazinyl; OH; -N(Y₁)(Y₂); C₁-C₁₀ alkyl
optionally substituted with 1 thru 3 substituents which
can be the same or different and are selected from
halogen, hydroxy, C₁-C₄ alkoxy, C₁-C₄ thioalkoxy, and C₁-C₄
haloalkoxy; C₃-C₆ cycloalkyl optionally substituted with
1, 2, or 3 groups independently selected from C₁-C₃ alkyl
and halogen; C₁-C₄ alkoxy; phenyl, benzyl or phenethyl
each of which is optionally substituted with halogen, C₁-
C₄ alkyl, C₁-C₄ alkoxy, CN or NO₂; wherein

5

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X-XIII

25

A₃ and A₄ are independently H, F, Cl, Br, or I;

R₅ is selected from cyclopropyl; cyclobutyl, cyclopentyl;
cyclohexyl; pyridyl, thiazolyl, pyrazolyl, or pyrazinyl
each of which is optionally substituted with 1, 2, or 3
groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy,
5 halogen, C₁-C₄ haloalkyl, or OH; piperidinyl,
dihydropyridazinonyl, pyrrolidinonyl,
thioxothiazolidinonyl, isoxazolyl, imidazolyl, or indolyl
each of which is optionally substituted with 1, or 2
groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy,
10 halogen, or C₂-C₄ alkanoyl; phenyl optionally substituted
with 1, 2, 3, or 4 groups that are independently halogen,
OH, C₁-C₄ alkyl, C₁-C₄ alkoxy, or C₁-C₂ haloalkyl; and
-NR₆R₇.

15 Preferred compounds of formula X-XIII include those
wherein

R₂₀ at each occurrence is independently H or C₁-C₄ alkyl;

X is C₁ or C₂ alkylidenyl;

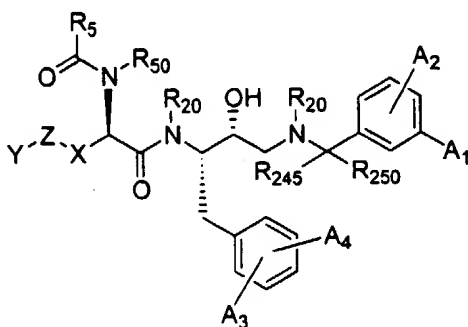
Z is SO₂; SO; S; or C(O); and

20 Y is phenyl; C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3
halogen; or OH; or

Y is -N(Y₁)(Y₂); wherein

Y₁ and Y₂ are independently H or C₁-C₄ alkyl.

25 More preferred compounds of formula X-XIII include those
of formula X-XIV:



X-XIV.

Preferred compounds of formulas X-XIII and X-XIV include those wherein

A₁ is C₁-C₄ alkyl, C₂ alkynyl, or I;

5 R₅₀ is H or C₁-C₄ alkyl;

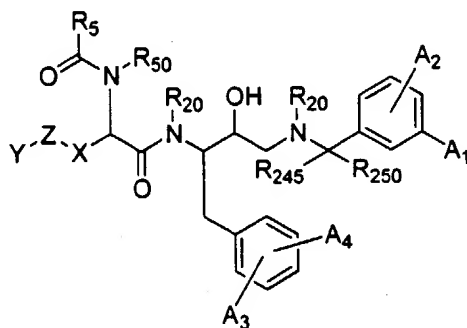
A₂ is H, C₁-C₄ alkyl, C₁-C₄ alkoxy, OCF₃, CF₃ or OH;

A₃ and A₄ are independently H, F, Cl, Br, or I.

Even more preferred compounds of formulas X-XIII and X-XIV
10 include those wherein

R₂₄₅ and R₂₅₀ are both hydrogen or R₂₄₅ and R₂₅₀ form a cyclopropyl group.

Other preferred compounds of formula X-XII include those
15 of formula X-XV:



X-XV

wherein

A₁ is H, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₂ alkynyl, or I;

20 A₂ is H, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, C₁-C₄ haloalkyl or OH;

A₃ and A₄ are independently H, F, Cl, Br, or I;

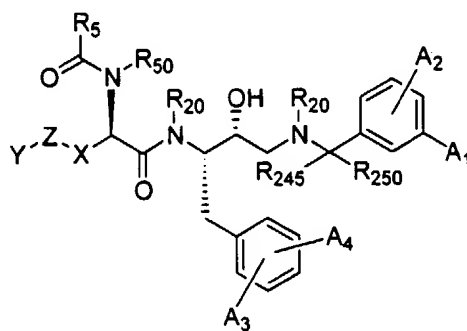
R₅ is C₁-C₆ alkyl optionally substituted with 1, 2, or 3 groups that are independently halogen, -NR₆R₇, C₁-C₄ alkoxy, piperidiny, pyrrolidiny, pyridyl, phenyl, C₃-C₆ cycloalkyl, S-C₁-C₄ alkyl, SO₂-C₁-C₄ alkyl, CO₂H, CONR₆R₇, CO₂-C₁-C₄ alkyl, or phenyloxy; and -NR₆R₇ wherein

25

R₆ and R₇ are independently selected from the group consisting of H, C₁-C₄ alkyl, C₂-C₆ alkanoyl, phenyl, and -SO₂-C₁-C₄ alkyl.

- 5 Preferred compounds of formula X-XV include those wherein
 R₂₀ at each occurrence is independently H or C₁-C₄ alkyl;
 X is C₁ or C₂ alkylidenyl;
 Z is SO₂; SO; S; or C(O); and
 Y is phenyl; C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3
 10 halogen; or OH; or
 Y is -N(Y₁)(Y₂); wherein
 Y₁ and Y₂ are independently H or C₁-C₄ alkyl.

- More preferred compounds of formula X-XV include those of
 15 formula X-XVI:



XVI.

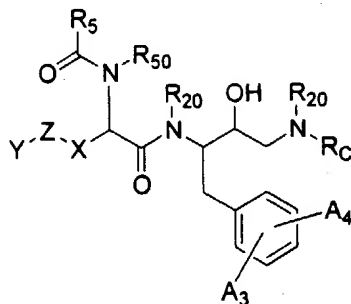
- Preferred compounds of formulas X-XV and X-XVI include
 20 those wherein
 A₁ is C₁-C₄ alkyl;
 R₅₀ is H or C₁-C₄ alkyl;
 A₂ is H, C₁-C₄ alkyl, C₁-C₄ alkoxy, OCF₃, CF₃ or OH;
 A₃ and A₄ are independently H, F, Cl, Br, or I.

25

More preferred compounds of formulas X-XV and X-XVI
 include those wherein

R₂₄₅ and R₂₅₀ are both hydrogen or R₂₄₅ and R₂₅₀ form a cyclopropyl group.

Other preferred compounds of formula X-XII include those
5 of formula X-XVII:



X-XVII

wherein

R_C is C₃-C₈ alkyl, cyclopropyl, cyclopentyl, cyclohexyl, or -
10 (C₁-C₄)alkyl-cyclopropyl;
A₃ and A₄ are independently H, F, Cl, Br, or I;
R₅ is selected from cyclopropyl; cyclopentyl; cyclohexyl;
pyridyl, thiazolyl, pyrazolyl, or pyrazinyl each of which
is optionally substituted with 1, 2, or 3 groups that are
15 independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, C₁-C₄
haloalkyl, or OH; piperidinyl, dihydropyridazinonyl,
pyrrolidinonyl, thioxothiazolidinonyl, isoxazolyl,
imidazolyl, or indolyl each of which is optionally
substituted with 1, or 2 groups that are independently C₁-
20 C₄ alkyl, C₁-C₄ alkoxy, halogen, or C₂-C₄ alkanoyl; phenyl
optionally substituted with 1, 2, 3, or 4 groups that are
independently halogen, OH, C₁-C₄ alkyl, C₁-C₄ alkoxy, or
C₁-C₂ haloalkyl; and -NR₆R₇.

25 Preferred compounds of formula X-XVII include those
wherein

R₂₀ at each occurrence is independently H or C₁-C₄ alkyl;
X is C₁ or C₂ alkylidenyl;
Z is SO₂; SO; S; or C(O); and

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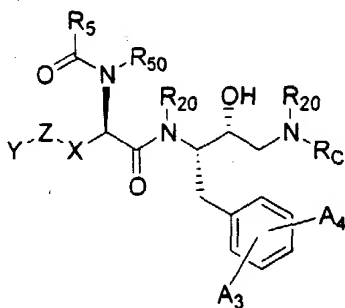
Y is phenyl; C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 halogen; or OH; or

Y is -N(Y₁)(Y₂); wherein

Y₁ and Y₂ are independently H or C₁-C₄ alkyl.

5

More preferred compounds of formula X-XVII include those of formula X-XVIII:



X-XVIII.

10

Preferred compounds of formulas X-XVII and X-XVIII include those wherein

R₅₀ is H or C₁-C₄ alkyl;

A₃ and A₄ are independently H, F, Cl, Br, or I.

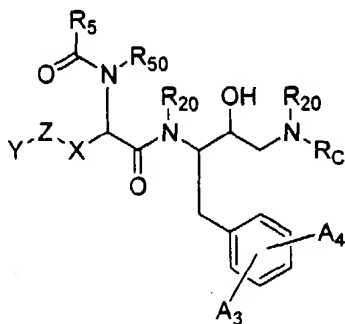
15

More preferred compounds of formulas X-XVII and X-XVIII include those wherein

R₂₄₅ and R₂₅₀ are both hydrogen or R₂₄₅ and R₂₅₀ form a cyclopropyl group.

20

Other preferred compounds of formula X-XII include those of formula X-XIX:



X-XIX

wherein

R_C is C_3 - C_8 alkyl, cyclopropyl, cyclopentyl, cyclohexyl, or -
(C_1 - C_4)alkyl-cyclopropyl;

5 A_3 and A_4 are independently H, F, Cl, Br, or I;

R_5 is C_1 - C_6 alkyl optionally substituted with 1, 2, or 3 groups
that are independently halogen, $-NR_6R_7$, C_1 - C_4 alkoxy,
piperidinyl, pyrrolidinyl, pyridyl, phenyl, C_3 - C_6
cycloalkyl, S- C_1 - C_4 alkyl, SO_2 - C_1 - C_4 alkyl, CO_2H , $CONR_6R_7$,
10 CO_2 - C_1 - C_4 alkyl, or phenyloxy; wherein

R_6 and R_7 are independently selected from the group
consisting of H, C_1 - C_4 alkyl, C_2 - C_6 alkanoyl,
phenyl, and $-SO_2$ - C_1 - C_4 alkyl.

15 Preferred compounds of formula X-XIX include those wherein

R_{20} at each occurrence is independently H or C_1 - C_4 alkyl;

X is C_1 or C_2 alkylidenyl;

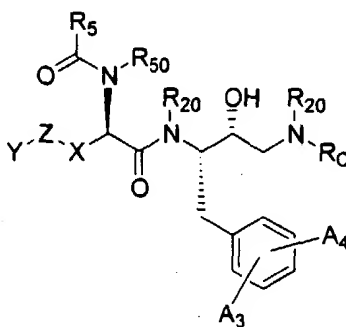
Z is SO_2 ; SO; S; or C(O); and

Y is phenyl; C_1 - C_{10} alkyl optionally substituted with 1, 2, or 3
20 halogen; or OH; or

Y is $-N(Y_1)(Y_2)$; wherein

Y_1 and Y_2 are independently H or C_1 - C_4 alkyl.

25 Preferred compounds of formula X-XIX include those of
formula X-XX:



X-XX.

Preferred compounds of formulas X-XIX and X-XX include those wherein

R₅₀ is H or C₁-C₄ alkyl;

A₃ and A₄ are independently H, F, Cl, Br, or I.

5

More preferred compounds of formulas X-XIX and X-XX include those wherein

R₂₄₅ and R₂₅₀ are both hydrogen or R₂₄₅ and R₂₅₀ form a cyclopropyl group.

10

Representative compounds of formula X-XI are:

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-{(3,3,3-trifluoropropanoyl)-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-{(trifluoroacetyl)-D-alaninamide;

N~2~-acetyl-3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-{(pyridin-4-ylcarbonyl)-D-alaninamide;

3-(butylsulfonyl)-N~2~-{(cyclopropylcarbonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-{(beta-alanyl)-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-glycyl-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-{(N,N-

alaninamide;

N~1~-[(1S,2R)-3-(cyclopropylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-N~2~-[(cyclopropylcarbonyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~2~-acetyl-N~1~-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-methylbutyl)amino]-2-hydroxypropyl]-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~1~-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-3-[(1-propylbutyl)sulfonyl]-N~2~-(pyridin-4-ylcarbonyl)-D-alaninamide;

N~2~-[(5-bromopyridin-3-yl)carbonyl]-N~1~-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~2~-[(5-chloropyridin-3-yl)carbonyl]-N~1~-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~1~-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-N~2~-(3-fluorobenzoyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~1~-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-N~2~-[(5-methylpyridin-3-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~2~-phenylglycyl-N~1~-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~1~-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-3-[(1-propylbutyl)sulfonyl]-N~2~-[(3-(trifluoromethyl)-1H-pyrazol-4-yl)carbonyl]-D-alaninamide;

N~1~-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-N~2~-[(3-methyl-1H-pyrazol-5-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~1~-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-

ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]-N-2--[(pyridin-3-yl)carbonyl]-D-alaninamide trifluoroacetate;

N-1--((1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethylphenyl)cyclopropyl]amino]-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]-N-2--[(pyridin-4-yl)carbonyl]-D-alaninamide trifluoroacetate;

N-1--((1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethylphenyl)cyclopropyl]amino]-2-hydroxypropyl)-N-2--(3-hydroxybenzoyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide trifluoroacetate;

N-1--((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]-N-2--[(pyridin-3-yl)carbonyl]-D-alaninamide;

N-1--((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N-2--(3-hydroxybenzoyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N-2--(cyclopropylcarbonyl)-N-1--((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N-1--((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N-2--propionyl-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

3-[butylsulfonyl]-N-1--((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N-2--[(pyridin-3-yl)carbonyl]-D,L-alaninamide;

N-1--((1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethylphenyl)cyclopropyl]amino]-2-hydroxypropyl)-N-2--(3-hydroxybenzoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide trifluoroacetate;

N-1--((1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethylphenyl)cyclopropyl]amino]-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]-N-2--[(pyridin-4-yl)carbonyl]-D-

N~1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2--[(1H-pyrazol-4-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2--[(1H-imidazol-5-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2--(1H-imidazol-4-ylacetyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-N~2--[(pyrazin-2-yl)carbonyl]-D,L-alaninamide;

N~1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2--[(3,5-dihydroxypyridin-4-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2--[(6-hydroxypyridin-3-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~2--[(6-chloropyridin-3-yl)carbonyl]-N~1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-N~2--[(pyridin-4-yl)carbonyl]-D,L-alaninamide;

N~1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2--[(pyridin-3-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-N~2--[(pyridin-2-yl)carbonyl]-D,L-alaninamide;

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N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N-2--[1H-indole-6-carbonyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-N-2--(2,3,4-trimethoxybenzoyl)-D,L-alaninamide;

N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N-2--[(pyridin-2-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N-2--(3-hydroxybenzoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide

N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N-2--(3-methylbenzoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N-2--(3-ethylbenzoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N-2--(3-chlorobenzoyl)-N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N-2--(4-methylbenzoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N-2--(4-methoxybenzoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N-2--(4-trifluoromethylbenzoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N-2--(cyclohexylcarbonyl)-N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-

[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~2~(benzoyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~2~(benzoyl)-N~1~-{(1S,2R)-3-(cyclopropylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~- (phenylacetyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~- (3-phenylpropanoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N-(3-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)amino)-3-oxo-2-[(1-propylbutyl)sulfonyl)methyl)propyl)benzamide;

N~1~-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N~2~- (cyclopropylacetyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N~2~- [(methylsulfonyl)acetyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N~2~- [(methylthio)acetyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide

N~1~-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N~2~- (4-hydroxy-4-oxobutanoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N~2~- [4-(methylamino)-4-oxobutanoyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1~-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N~2~- (4-methoxy-4-oxobutanoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N-(methylsulfonyl)glycyl-N-1--{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N-2--acetyl-N-1--{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-3-(phenylsulfonyl)-D,L-alaninamide;

N-[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-(2S)-2-[(4-methoxy-4-oxobutanoyl)amino]-5-oxo-5-piperidin-1-ylpentanamide;

(2R)-2-[[(benzyloxy)carbonyl]amino]-N-[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-5-oxo-5-piperidin-1-ylpentanamide;

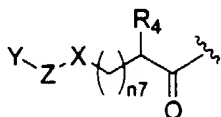
N-[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-(2R)-2-[(3-ethoxy-3-oxopropanoyl)amino]-5-oxo-5-piperidin-1-ylpentanamide;

N-1--{(1S,2R)-1-benzyl-3-[(3-methoxybenzyl)amino]-2-hydroxypropyl}-N-2--(4-methoxy-4-oxobutanoyl)-N-5~,N-5~-dipropyl-D-glutamamide;

N-[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-(2R)-2-[(4-methoxy-4-oxobutanoyl)amino]-5-oxo-5-piperidin-1-ylpentanamide; and

N-[(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl]-(2R)-2-[(5-methoxy-5-oxopentanoyl)amino]-5-oxo-5-piperidin-1-ylpentanamide and pharmaceutically acceptable salts thereof.

Other preferred compounds of formula X-XII include those of formula X-XXI, i.e., compounds of formula X-XII wherein R_N is of the formula:



5

wherein

n_7 is 0, 1, or 2;

R_4 is $-NHR_8$ or $-NH(CH_2)_{n6}-R_{4-1}$; wherein

N_6 is 0, 1, 2, or 3;

R_{4-1} is selected from the group consisting of $-\text{SO}_2-(\text{C}_1-\text{C}_8$
alkyl), $-\text{SO}-(\text{C}_1-\text{C}_8$ alkyl), $-\text{S}-(\text{C}_1-\text{C}_8$ alkyl), $-\text{S}-\text{CO}-$
(C_1-C_6 alkyl), $-\text{SO}_2-\text{NR}_{4-2}\text{R}_{4-3}$; $-\text{CO}-\text{C}_1-\text{C}_2$ alkyl; $-\text{CO}-\text{NR}_{4-3}$
 R_{4-4} ;

R_{4-2} and R_{4-3} are independently H, C_1-C_3 alkyl, or C_3-C_6
cycloalkyl;

R_{4-4} is C_1-C_4 alkyl, phenyl C_1-C_4 alkyl, C_2-C_4 alkanoyl,
or phenyl C_1-C_4 alkanoyl;

R_8 is selected from the group consisting of $-\text{SO}_2-$
heteroaryl optionally substituted with 1 or 2 groups
that are independently C_1-C_4 alkyl or halogen; $-\text{SO}_2-$
phenyl; $-\text{SO}_2$ -heterocycloalkyl; $-\text{C}(\text{O})\text{NHR}_9$;
heterocycloalkyl; $-\text{S}-\text{C}_2-\text{C}_4$ alkanoyl; wherein

R_9 is phenyl C_1-C_4 alkyl, C_1-C_6 alkyl, or H;

X is C_1-C_4 alkylidenyl optionally optionally substituted with
1, 2, or 3 methyl groups; or $-\text{NR}_{4-6}-$; or

R_4 and R_{4-6} combine to form $-(\text{CH}_2)_{n_{10}}-$, wherein
 n_{10} is 1, 2, 3, or 4;

Z is SO_2 ; SO; S; or C(O);

Y is H; C_1-C_4 haloalkyl; C_5-C_6 heterocycloalkyl containing at
least one N, O, or S; phenyl; OH; $-\text{N}(\text{Y}_1)(\text{Y}_2)$; C_1-C_{10} alkyl
optionally substituted with 1 thru 3 substituents which
can be the same or different and are selected from
halogen, hydroxy, alkoxy, thioalkoxy, and haloalkoxy; C_3-
 C_8 cycloalkyl optionally substituted with 1, 2, or 3
groups independently selected from C_1-C_3 alkyl, and
halogen; alkoxy; phenyl optionally substituted with
halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, CN or NO_2 ; or phenyl C_1-
 C_4 alkyl optionally substituted with halogen, C_1-C_4 alkyl,
 C_1-C_4 alkoxy, CN or NO_2 ; wherein

Y_1 and Y_2 are the same or different and are H; C_1-C_{10} alkyl
optionally substituted with 1, 2, or 3 substituents
selected from halogen, C_1-C_4 alkoxy, C_3-C_8 cycloalkyl,

and OH; C₂-C₆ alkenyl; C₂-C₆ alkanoyl; phenyl; -SO₂-C₁-C₄ alkyl; phenyl C₁-C₄ alkyl; or C₃-C₈ cycloalkyl C₁-C₄ alkyl; or

-N(Y₁)(Y₂) forms a ring selected from piperazinyl, piperidinyl, morpholinyl, and pyrrolidinyl, wherein each ring is optionally substituted with 1, 2, 3, or 4 groups that are independently C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkoxy C₁-C₆ alkyl, or halogen; and

R₂₀ at each occurrence is independently hydrogen, C₁-C₆ alkyl, C₁-C₆ alkoxy C₁-C₆ alkyl, halo C₁-C₆ alkyl, or C₁-C₆ alkanoyl, each of which is unsubstituted or substituted with 1, or 2 groups independently selected from halogen, C₁-C₆ alkyl, hydroxy, C₁-C₆ alkoxy, NH₂, and -R₂₆-R₂₇, wherein

R₂₆ is -C(O)-, -SO₂-, -CO₂-, -C(O)NH-, or -C(O)N(C₁-C₆ alkyl)-;

R₂₇ is C₁-C₆ alkyl, C₁-C₆ alkoxy, aryl C₁-C₆ alkyl, heterocycloalkyl, or heteroaryl, wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, halo C₁-C₆ alkyl, hydroxy C₁-C₆ alkyl, -C(O)NH₂, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)(C₁-C₆ alkyl), -C(O)NH(C₁-C₆ alkyl), or -C(O)N(C₁-C₆ alkyl)(C₁-C₆ alkyl).

Preferred compounds of formula X-XXI include those wherein R₂ and R₃ are independently H or C₁-C₆ alkyl optionally substituted with 1, or 2 substituents selected from halogen, OH, SH, C≡N, CF₃, and C₁-C₃ alkoxy; and

R_C is C₁-C₈ alkyl optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of R₂₀₅, -OC=ONR₂₃₅R₂₄₀, -S(=O)₀₋₂(C₁-C₆ alkyl), -SH, -C=ONR₂₃₅R₂₄₀, and -S(=O)₂NR₂₃₅R₂₄₀; -(CH₂)₀₋₃-(C₃-C₈) cycloalkyl wherein the cycloalkyl is optionally substituted with 1, 2, or 3

groups independently selected from the group consisting of
R₂₀₅, -CO₂H, and -CO₂-(C₁-C₄ alkyl); -(CR₂₄₅R₂₅₀)₀₋₄-phenyl;
-(CR₂₄₅R₂₅₀)₀₋₄-heteroaryl; -(CR₂₄₅R₂₅₀)₀₋₄-heterocycloalkyl; or
-(CH₂)₀₋₁-CH(C₁-C₄ hydroxyalkyl)-(CH₂)₀₋₁-heteroaryl; wherein
5 each aryl is optionally substituted with 1, 2, or 3 R₂₀₀;
each heteroaryl is optionally substituted with 1, 2, 3, or

4 R₂₀₀;

each heterocycloalkyl is optionally substituted with 1, 2,
3, or 4 R₂₁₀;

10 R₂₀₀ at each occurrence is independently C₁-C₆ alkyl
optionally substituted with 1, 2, or 3 R₂₀₅ groups;
OH; -NO₂; halogen; -CO₂H; C≡N; -(CH₂)₀₋₄-CO-NR₂₂₀R₂₂₅;
-(CH₂)₀₋₄-CO-(C₁-C₁₂ alkyl); -(CH₂)₀₋₄-CO₂R₂₁₅; or -(CH₂)₀₋₄-O-(C₁-C₆ alkyl optionally substituted with 1, 2, 3,
15 or 5 -F);

R₂₀₅ at each occurrence is independently C₁-C₆ alkyl,
halogen, -OH, -O-phenyl, -SH, -C≡N, -CF₃, C₁-C₆
alkoxy, NH₂, NH(C₁-C₆ alkyl), or N-(C₁-C₆ alkyl)(C₁-C₆
alkyl);

20 R₂₁₀ at each occurrence is independently C₁-C₆ alkyl
optionally substituted with 1, 2, or 3 R₂₀₅ groups;
halogen; C₁-C₆ alkoxy; C₁-C₆ haloalkoxy; -NR₂₂₀R₂₂₅; OH;
C≡N; C₃-C₇ cycloalkyl optionally substituted with 1,
2, or 3 R₂₀₅ groups; -CO-(C₁-C₄ alkyl); -SO₂-NR₂₃₅R₂₄₀; -
25 CO-NR₂₃₅R₂₄₀; -SO₂-(C₁-C₄ alkyl); or =O; wherein

R₂₁₅ at each occurrence is independently C₁-C₆ alkyl,
-(CH₂)₀₋₂-(phenyl), C₃-C₇ cycloalkyl, and -(CH₂)₀₋₂-
(heteroaryl), or -(CH₂)₀₋₂-(heterocycloalkyl); wherein
the phenyl group at each occurrence is optionally
30 substituted with 1, 2, or 3 groups that are
independently R₂₀₅ or R₂₁₀; wherein the
heterocycloalkyl group at each occurrence is
optionally substituted with 1, 2, or 3 R₂₁₀; wherein

each heteroaryl group at each occurrence is optionally substituted with 1, 2, or 3 R_{210} ;

R_{220} and R_{225} at each occurrence are independently -H, -C₁-C₆ alkyl, hydroxy C₁-C₄ alkyl, halo C₁-C₄ alkyl; -C₃-C₇ cycloalkyl, or -(C₁-C₆ alkyl)-O-(C₁-C₃ alkyl);

R_{235} and R_{240} at each occurrence are independently H, or C₁-C₆ alkyl;

R_{245} and R_{250} at each occurrence are independently H, C₁-C₄ alkyl, C₁-C₄ hydroxyalkyl, C₁-C₄ alkoxy, or C₁-C₄ haloalkoxy, or

R_{245} and R_{250} are taken together with the carbon to which they are attached to form a carbocycle of 3, 4, 5, or 6 carbon atoms.

More preferred compounds of formula X-XXI include those wherein

R_1 is benzyl which is optionally substituted with 1, 2, 3, or 4 groups independently selected from C₁-C₄ alkyl optionally substituted with 1, or 2 substituents selected from halogen, -OH, -SH, NH₂, NH(C₁-C₆ alkyl), N-(C₁-C₆ alkyl)(C₁-C₆ alkyl), -C≡N, -CF₃, and C₁-C₃ alkoxy; halogen; C₁-C₄ alkoxy; and OH.

Other more preferred compounds of formula X-XXI include those wherein

n_7 is 0, 1, or 2;

R_4 is -NHR₈ or -NH(CH₂) _{n_6} -R₄₋₁; wherein

N_6 is 0, 1, or 2;

R_{4-1} is selected from the group consisting of -SO₂-(C₁-C₈ alkyl), -S-CO-(C₁-C₆ alkyl), -SO₂-NR₄₋₂R₄₋₃; -CO-C₁-C₂ alkyl; -CO-NR₄₋₃R₄₋₄;

R_{4-2} and R_{4-3} are independently H, or C₁-C₃ alkyl;

R_{4-4} is C₁-C₄ alkyl, phenyl C₁-C₄ alkyl, C₂-C₄ alkanoyl, or phenyl C₁-C₄ alkanoyl;

R_8 is $-SO_2$ -thienyl optionally substituted with 1 or 2 groups that are independently C_1 - C_4 alkyl or halogen; $-SO_2$ -phenyl, $-SO_2$ -piperidinyl, $-SO_2$ -pyrrolidinyl, $-C(O)NHR_9$, morpholinyl, or $-S-C_2-C_4$ alkanoyl, wherein R_9 is phenyl C_1 - C_4 alkyl, C_1 - C_6 alkyl, or H.

Even more preferred compounds of formula X-XXI include those wherein

R_{20} at each occurrence is independently hydrogen, C_1 - C_6 alkyl, C_1 - C_2 alkoxy C_1 - C_4 alkyl, C_2 - C_6 alkanoyl, each of which is unsubstituted or substituted with 1 or 2 groups independently selected from halogen, hydroxy, C_1 - C_4 alkoxy, tertiary-butoxy carbonyl, benzyloxycarbonyl, and NH_2 ;

R_C is C_1 - C_8 alkyl optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of R_{205} , $-SH$, $-C=ONR_{235}R_{240}$, and $-S(=O)_2NR_{235}R_{240}$; $-(CH_2)_{0-3}-(C_3-C_6)$ cycloalkyl wherein the cycloalkyl is optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of R_{205} , $-CO_2H$, and $-CO_2-(C_1-C_4)$ alkyl); $-(CR_{245}R_{250})_{0-4}$ -phenyl optionally substituted with 1, 2, or 3 R_{200} ; $-(CR_{245}R_{250})_{0-3}$ -pyridyl; $-(CR_{245}R_{250})_{0-3}$ -pyridazinyl; $-(CR_{245}R_{250})_{0-3}$ -pyrimidinyl; $-(CR_{245}R_{250})_{0-3}$ -pyrazinyl; $-(CR_{245}R_{250})_{0-3}$ -furyl; $-(CR_{245}R_{250})_{0-3}$ -indolyl; $-(CR_{245}R_{250})_{0-3}$ -thienyl; $-(CR_{245}R_{250})_{0-3}$ -pyrrolyl; $-(CR_{245}R_{250})_{0-3}$ -pyrazolyl; $(CR_{245}R_{250})_{0-3}$ -benzoxazolyl; $-(CR_{245}R_{250})_{0-3}$ -imidazolyl; each of the above heteroaryl groups is optionally substituted with 1, 2, 3, or 4 R_{200} ; $-(CR_{245}R_{250})_{0-3}$ -imidazolidinyl; $(CR_{245}R_{250})_{0-3}$ -tetrahydrofuryl; $(CR_{245}R_{250})_{0-3}$ -tetrahydropyranyl; $(CR_{245}R_{250})_{0-3}$ -piperazinyl; $(CR_{245}R_{250})_{0-3}$ -pyrrolidinyl; $(CR_{245}R_{250})_{0-3}$ -piperidinyl; $(CR_{245}R_{250})_{0-3}$ -indolinyl; each of the above heterocycloalkyl groups is optionally substituted with 1, 2, 3, or 4 R_{210} ; $(CH_2)_{0-1}$ -

CH((CH₂)₀₋₄-OH)-(CH₂)₀₋₁-phenyl; or -(CH₂)₀₋₁-CH(C₁-C₄
hydroxyalkyl)-(CH₂)₀₋₁-pyridyl;

R₂₀₀ at each occurrence is independently C₁-C₆ alkyl
optionally substituted with 1, 2, or 3 R₂₀₅ groups;
5 OH; -NO₂; halogen; -CO₂H; C≡N; -(CH₂)₀₋₄-CO-NR₂₂₀R₂₂₅;
-(CH₂)₀₋₄-CO-(C₁-C₈ alkyl); -(CH₂)₀₋₄-CO₂R₂₁₅; or -(CH₂)₀₋₄-O-(C₁-C₆ alkyl optionally substituted with 1, 2, 3,
or 5 -F);

R₂₀₅ at each occurrence is independently C₁-C₆ alkyl,
10 halogen, -OH, -O-phenyl, -SH, -C≡N, -CF₃, C₁-C₆
alkoxy, NH₂, NH(C₁-C₆ alkyl), or N-(C₁-C₆ alkyl)(C₁-C₆
alkyl);

R₂₁₀ at each occurrence is independently C₁-C₆ alkyl
optionally substituted with 1 or 2 R₂₀₅ groups;
15 halogen; C₁-C₄ alkoxy; C₁-C₄ haloalkoxy; -NR₂₂₀R₂₂₅; OH;
C≡N; C₃-C₇ cycloalkyl optionally substituted with 1
or 2 R₂₀₅ groups; -CO-(C₁-C₄ alkyl); -SO₂-NR₂₃₅R₂₄₀; -CO-
NR₂₃₅R₂₄₀; -SO₂-(C₁-C₄ alkyl); or =O; wherein

R₂₁₅ at each occurrence is independently C₁-C₆ alkyl,
20 -(CH₂)₀₋₂-(phenyl), C₃-C₆ cycloalkyl, -(CH₂)₀₋₂-
(pyridyl), -(CH₂)₀₋₂-(pyrrolyl), -(CH₂)₀₋₂-
(imidazolyl), -(CH₂)₀₋₂-(pyrimidyl), -(CH₂)₀₋₂-
(pyrrolidinyl), -(CH₂)₀₋₂-(imidazolidinyl), -(CH₂)₀₋₂-
(piperazinyl), -(CH₂)₀₋₂-(piperidinyl), or -(CH₂)₀₋₂-
25 (morpholinyl); wherein the phenyl group at each
occurrence is optionally substituted with 1 or 2
groups that are independently R₂₀₅ or R₂₁₀; wherein
each heterocycloalkyl group at each occurrence is
optionally substituted with 1 or 2 R₂₁₀; wherein each
30 heteroaryl group at each occurrence is optionally
substituted with 1 or 2 R₂₁₀;

R₂₂₀ and R₂₂₅ at each occurrence are independently -H, -C₁-
C₄ alkyl, hydroxy C₁-C₄ alkyl, halo C₁-C₄ alkyl; -C₃-C₆
cycloalkyl, or -(C₁-C₄ alkyl)-O-(C₁-C₂ alkyl);

- R₂₃₅ and R₂₄₀ at each occurrence are independently H, or C₁-C₆ alkyl;
- R₂₄₅ and R₂₅₀ at each occurrence are independently H, C₁-C₄ alkyl, C₁-C₄ hydroxyalkyl, C₁-C₄ alkoxy, or C₁-C₄ haloalkoxy, or
- R₂₄₅ and R₂₅₀ are taken together with the carbon to which they are attached to form a carbocycle of 3, 5, or 6 carbon atoms.
- Still other more preferred compounds of formula X-XXI include those wherein
- X is-C₁-C₃ alkylidenyl optionally optionally substituted with 1 or 2 methyl groups;
- Z is SO₂; SO; S; or C(O);
- Y is H; C₁-C₄ haloalkyl; pyrrolidinyl; piperidinyl; imidazolidinyl; piperazinyl; OH; -N(Y₁)(Y₂); C₁-C₁₀ alkyl optionally substituted with 1 thru 3 substituents which can be the same or different and are selected from halogen, hydroxy, C₁-C₄ alkoxy, C₁-C₄ thioalkoxy, and C₁-C₄ haloalkoxy; C₃-C₆ cycloalkyl optionally substituted with 1, 2, or 3 groups independently selected from C₁-C₃ alkyl and halogen; C₁-C₄ alkoxy; phenyl, benzyl or phenethyl each of which is optionally substituted with halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, CN or NO₂; wherein
- Y₁ and Y₂ are independently H; C₁-C₆ alkyl optionally substituted with 1, 2, or 3 substituents selected from halogen, C₁-C₄ alkoxy, C₃-C₆ cycloalkyl, and OH; C₂-C₆ alkanoyl; phenyl; -SO₂-C₁-C₄ alkyl; phenyl C₁-C₄ alkyl; or C₃-C₆ cycloalkyl C₁-C₄ alkyl; or
- N(Y₁)(Y₂) forms a ring selected from piperazinyl, piperidinyl, morpholinyl, and pyrrolidinyl, wherein each ring is optionally substituted with 1, 2, or 3 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ alkoxy C₁-C₄ alkyl, or halogen; and

R₂ and R₃ are independently H or C₁-C₄ alkyl.

Other more preferred compounds of formula X-XXI include those wherein

- 5 n₇ is 0, 1, or 2;
R₄ is -NHR₈ or -NH(CH₂)_{n₆}-R₄₋₁; wherein
N₆ is 0, 1, or 2;
R₄₋₁ is selected from the group consisting of -SO₂-(C₁-C₈
alkyl), -SO₂-NR₄₋₂R₄₋₃; -CO-C₁-C₂ alkyl; -CO-NR₄₋₃R₄₋₄;
10 R₄₋₂ and R₄₋₃ are independently H, or C₁-C₃ alkyl;
R₄₋₄ is C₁-C₄ alkyl, phenyl C₁-C₄ alkyl, C₂-C₄ alkanoyl,
or phenyl C₁-C₄ alkanoyl;
R₈ is -SO₂-thienyl optionally substituted with 1 or 2
groups that are independently C₁-C₄ alkyl or halogen;
15 -SO₂-phenyl, -SO₂-piperidinyl, -SO₂-pyrrolidinyl,
-C(O)NHR₉, or -S-C₂-C₄ alkanoyl, wherein
R₉ is phenyl C₁-C₄ alkyl, C₁-C₄ alkyl, or H;
R₂₀ at each occurrence is independently hydrogen, C₁-C₆ alkyl,
C₂-C₆ alkanoyl, tertiary-butoxy carbonyl, and
20 benzyloxycarbonyl;
R_C is C₁-C₈ alkyl optionally substituted with 1 or 2 groups
independently selected from R₂₀₅, and -SH; -(CH₂)₀₋₃-(C₃-C₆)
cycloalkyl wherein the cycloalkyl is optionally
substituted with 1 R₂₀₅ group; -(CR₂₄₅R₂₅₀)₀₋₃-phenyl
25 optionally substituted with 1 or 2 R₂₀₀; -(CR₂₄₅R₂₅₀)₀₋₃-
pyridyl; -(CR₂₄₅R₂₅₀)₀₋₃-pyrrolyl; (CR₂₄₅R₂₅₀)₀₋₃-benzoxazolyl;
-(CR₂₄₅R₂₅₀)₀₋₃-imidazolyl; each of the above heteroaryl
groups is optionally substituted with 1 or 2 R₂₀₀; -
(CR₂₄₅R₂₅₀)₀₋₃-imidazolidinyl; (CR₂₄₅R₂₅₀)₀₋₃-tetrahydrofuryl;
30 (CR₂₄₅R₂₅₀)₀₋₃-tetrahydropyranyl; (CR₂₄₅R₂₅₀)₀₋₃-pyrrolidinyl;
(CR₂₄₅R₂₅₀)₀₋₃-piperidinyl; each of the above
heterocycloalkyl groups is optionally substituted with 1
or 2 R₂₁₀; (CH₂)₀₋₁-CH((CH₂)₀₋₄-OH)-(CH₂)₀₋₁-phenyl; or -(CH₂)₀₋₁-
CH(C₁-C₄ hydroxyalkyl)-(CH₂)₀₋₁-pyridyl;

- R₂₀₀ at each occurrence is independently C₁-C₄ alkyl optionally substituted with 1, 2, or 3 R₂₀₅ groups; OH; NO₂; halogen; CO₂H; C≡N; or -(CH₂)₀₋₄-O-(C₁-C₆ alkyl optionally substituted with 1, 2, 3, or 5 -F);
- 5 R₂₀₅ at each occurrence is independently C₁-C₆ alkyl, halogen, OH, -O-phenyl, SH, C≡N, CF₃, C₁-C₆ alkoxy, NH₂, NH(C₁-C₆ alkyl), or N(C₁-C₆ alkyl)(C₁-C₆ alkyl);
- R₂₁₀ at each occurrence is independently C₁-C₆ alkyl optionally substituted with 1 R₂₀₅ group; halogen; C₁-C₄ alkoxy; C₁-C₄ haloalkoxy; OH; C≡N; or =O; wherein
- 10 R₂₃₅ and R₂₄₀ at each occurrence are independently H, or C₁-C₆ alkyl;
- R₂₄₅ and R₂₅₀ at each occurrence are independently H, C₁-C₄ alkyl, C₁-C₄ hydroxyalkyl, C₁-C₄ alkoxy, or
- 15 R₂₄₅ and R₂₅₀ are taken together with the carbon to which they are attached to form a carbocycle of 3, 5, or 6 carbon atoms;
- X is-C₁-C₃ alkylidenyl;
- Z is SO₂; SO; S; or C(O);
- 20 Y is H; C₁-C₄ haloalkyl; pyrrolidinyl; piperidinyl; imidazolidinyl; piperazinyl; OH; -N(Y₁)(Y₂); C₁-C₁₀ alkyl optionally substituted with 1 thru 3 substituents which can be the same or different and are selected from halogen, hydroxy, C₁-C₄ alkoxy, C₁-C₄ thioalkoxy, and C₁-C₄ haloalkoxy; C₃-C₆ cycloalkyl optionally substituted with
- 25 1, 2, or 3 groups independently selected from C₁-C₃ alkyl and halogen; C₁-C₄ alkoxy; phenyl, benzyl or phenethyl each of which is optionally substituted with halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, CN or NO₂; wherein
- 30 Y₁ and Y₂ are indepenently H; C₁-C₆ alkyl optionally substituted with 1, 2, or 3 substituents selected from halogen, C₁-C₄ alkoxy, C₃-C₆ cycloalkyl, and OH; C₂-C₆ alkanoyl; phenyl; -SO₂-C₁-C₄ alkyl; phenyl C₁-C₄ alkyl; or cyclopropyl C₁-C₄ alkyl; or

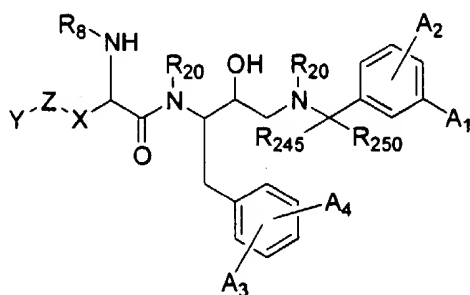
-N(Y₁)(Y₂) forms a ring selected from piperaziny1,
piperidinyl, and pyrrolidinyl, wherein each ring is
optionally substituted with 1 or 2 groups that are
independently C₁-C₄ alkyl, C₁-C₄ alkoxy, or halogen;

5 R₂ and R₃ are independently H or C₁-C₄ alkyl; and

R₁ is benzyl which is optionally substituted with 1, 2, or 3
groups independently selected from C₁-C₄ alkyl optionally
substituted with 1 substituent selected from halogen, -OH,
-CF₃, and C₁-C₃ alkoxy; halogen; C₁-C₄ alkoxy; and OH.

10

Particularly preferred compounds of formula X-XXI include
those of formula X-XXII:



X-XXII

15 wherein

A₁ is H, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₂-C₆ alkynyl, or halogen;

A₂ is H, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, C₁-C₄
haloalkyl or OH;

A₃ and A₄ are independently C₁-C₄ alkyl, halogen, or H;

20 R₈ is -SO₂-thienyl optionally substituted with 1 or 2 groups
that are independently C₁-C₄ alkyl or halogen; -SO₂-phenyl,
-SO₂-piperidinyl, -SO₂-pyrrolidinyl, -C(O)NHR₉, or -S-C₂-C₄
alkanoyl, wherein

R₉ is phenyl C₁-C₄ alkyl, C₁-C₄ alkyl, or H.

25

Preferred compounds of formulas X-XXI and X-XXII include
those wherein

R₂₀ at each occurrence is independently H or C₁-C₄ alkyl;

X is C₁ or C₂ alkylidenyl;

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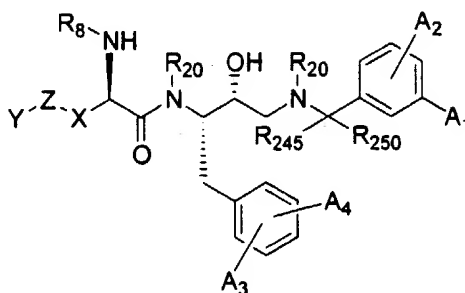
Z is SO₂; SO; S; or C(O); and

Y is phenyl; C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3
halogen; or OH; or

Y is -N(Y₁)(Y₂); wherein

5 Y₁ and Y₂ are independently H or C₁-C₄ alkyl.

Preferred compounds of formula X-XXII include those of
formula X-XXIII:



X-XXIII.

Preferred compounds of formulas X-XXII and X-XXIII include
those wherein

A₁ is C₁-C₄ alkyl, C₂ alkynyl, or I;

15 A₂ is H, C₁-C₄ alkyl, C₁-C₄ alkoxy, OCF₃, CF₃ or OH;

A₃ and A₄ are independently H or halogen; and

R₈ is -SO₂-thienyl optionally substituted with 1 or 2 groups
that are independently C₁-C₄ alkyl or halogen; -SO₂-phenyl;
or -C(O)NHR₉; wherein

20 R₉ is phenyl C₁-C₄ alkyl, C₁-C₄ alkyl, or H.

Other preferred compounds of formulas X-XXII and X-XXIII
include those wherein

R₂₄₅ and R₂₅₀ are both hydrogen or R₂₄₅ and R₂₅₀ form a cyclopropyl
25 group.

Other preferred compounds of formulas X-XXII and X-XXIII
include those wherein

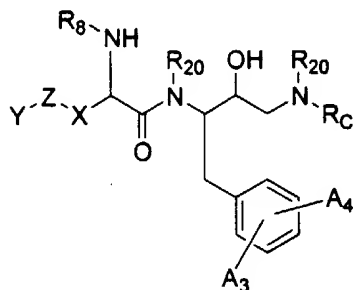
R₂₀ and A₂ are both hydrogen; and

A₃ and A₄ are independently halogen.

Still other preferred compounds of formulas X-XXII and X-XXIII include those wherein

5 A₃ and A₄ are meta to each other.

Other preferred compounds of formula X-XXI include those of formula X-XXIV:



X-XXIV

wherein

R_C is C₃-C₈ alkyl, cyclopropyl, cyclopentyl, cyclohexyl, or -
(C₁-C₄)alkyl-(C₃-C₆) cycloalkyl.

Preferred compounds of formula X-XXIV include those wherein

R₂₀ at each occurrence is independently H or C₁-C₄ alkyl;

X is C₁ or C₂ alkylidenyl;

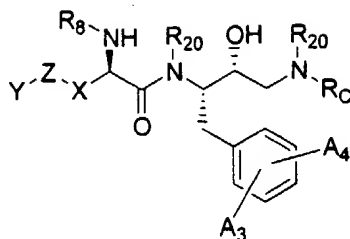
Z is SO₂; SO; S; or C(O); and

Y is phenyl; C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3
halogen; or OH; or

Y is -N(Y₁)(Y₂); wherein

Y₁ and Y₂ are independently H or C₁-C₄ alkyl.

More preferred compounds of formula X-XXIV include those of formula X-XXV:



X-XXV.

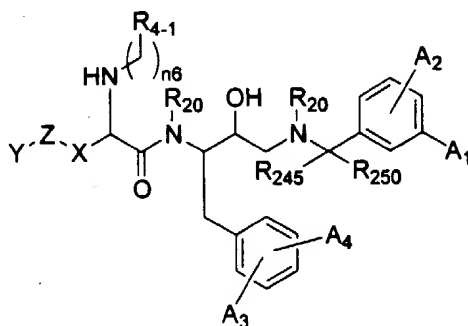
Preferred compounds of formulas X-XXIV and X-XXV include those wherein wherein

R_8 is $-SO_2$ -thienyl optionally substituted with 1 or 2 groups that are independently C_1 - C_4 alkyl or halogen; $-SO_2$ -phenyl; or $-C(O)NHR_9$; wherein R_9 is phenyl C_1 - C_4 alkyl, C_1 - C_4 alkyl, or H.

Other preferred compounds of formulas X-XXIV and X-XXV include those wherein R_{20} and A_2 are both hydrogen; and A_3 and A_4 are independently halogen.

More preferred compounds of formulas X-XXIV and X-XXV include those wherein A_3 and A_4 are meta to each other. Even more preferably, A_3 and A_4 are at the 3 and 5 positions of the benzene ring.

Other preferred compounds of formula X-XXI include those of formula X-XXVI:



X-XXVI

wherein

N_6 is 0, 1, or 2;

R_{4-1} is selected from the group consisting of $-SO_2-(C_1-C_8 \text{ alkyl})$,

$-SO_2-NR_{4-2}R_{4-3}$; $-CO-C_1-C_2 \text{ alkyl}$; $-CO-NR_{4-3}R_{4-4}$;

5 R_{4-2} and R_{4-3} are independently H, or $C_1-C_3 \text{ alkyl}$;

R_{4-4} is $C_1-C_4 \text{ alkyl}$, phenyl $C_1-C_4 \text{ alkyl}$, $C_2-C_4 \text{ alkanoyl}$, or phenyl $C_1-C_4 \text{ alkanoyl}$;

A_1 is H, $C_1-C_4 \text{ alkyl}$, $C_1-C_4 \text{ alkoxy}$, halogen or $C_2-C_6 \text{ alkynyl}$;

A_2 is H, $C_1-C_4 \text{ alkyl}$, $C_1-C_4 \text{ alkoxy}$, $C_1-C_4 \text{ haloalkoxy}$, C_1-C_4

10 haloalkyl or OH;

A_3 and A_4 are independently $C_1-C_4 \text{ alkyl}$, halogen, or H.

Preferred compounds of formula X-XXVI include those wherein

15 R_{20} at each occurrence is independently H or $C_1-C_4 \text{ alkyl}$;

X is C_1 or $C_2 \text{ alkylidenyl}$;

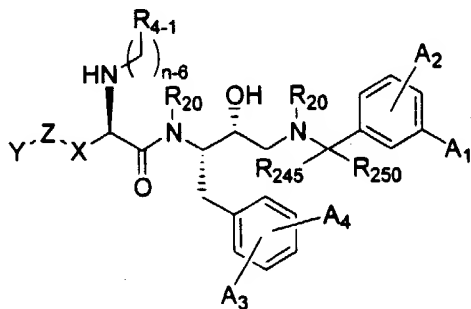
Z is SO_2 ; SO; S; or $C(O)$; and

Y is phenyl; $C_1-C_{10} \text{ alkyl}$ optionally substituted with 1, 2, or 3 halogen; or OH; or

20 Y is $-N(Y_1)(Y_2)$; wherein

Y_1 and Y_2 are independently H or $C_1-C_4 \text{ alkyl}$.

More preferred compounds of formula X-XXVI include those of formula X-XXVII:



X-XXVII

wherein

A_1 is $C_1-C_4 \text{ alkyl}$, $C_2 \text{ alkynyl}$ or I;

A_2 is H, $C_1-C_4 \text{ alkyl}$, $C_1-C_4 \text{ alkoxy}$, OCF_3 , CF_3 or OH;

A₃ and A₄ are independently H or halogen; and

N₆ is 0, 1, or 2;

R₄₋₁ is selected from the group consisting of -SO₂-(C₁-C₈ alkyl),

-SO₂-NR₄₋₂R₄₋₃; -CO-C₁-C₂ alkyl; -CO-NR₄₋₃R₄₋₄;

5 R₄₋₂ and R₄₋₃ are independently H, or C₁-C₃ alkyl;

R₄₋₄ is C₁-C₄ alkyl, phenyl C₁-C₄ alkyl, C₂-C₄ alkanoyl, or
phenyl C₁-C₄ alkanoyl.

10 Preferred compounds of formulas X-XXVI and X-XXVII include
those wherein

R₂₄₅ and R₂₅₀ are both hydrogen or R₂₄₅ and R₂₅₀ form a cyclopropyl
group.

15 More preferred compounds of formulas X-XXVI and X-XXVII
include those wherein

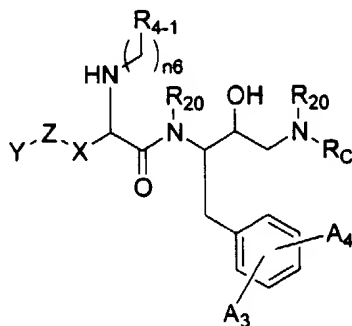
R₂₀ and A₂ are both hydrogen; and

A₃ and A₄ are independently halogen.

20 More preferred compounds of formulas X-XXVI and X-XXVII
include those wherein

A₃ and A₄ are meta to each other. More preferably, A₃ and A₄
are at the 3 and 5 positions of the phenyl ring.

25 Other preferred compounds of formula X-XXI include those
of formula X-XXVIII:



X-XXVIII

wherein

R_C is C_3 - C_8 alkyl, cyclopropyl, cyclopentyl, cyclohexyl, or
 -(C_1 - C_4)alkyl-(C_3 - C_6) cycloalkyl.

Preferred compounds of formula X-XXVIII include those

5 wherein

R_{20} at each occurrence is independently H or C_1 - C_4 alkyl;

X is C_1 or C_2 alkylidenyl;

Z is SO_2 ; SO; S; or C(O); and

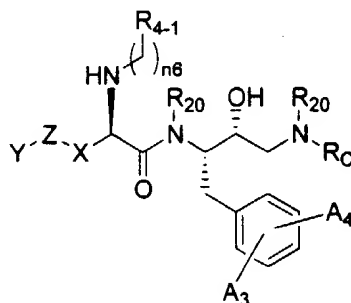
10 Y is phenyl; C_1 - C_{10} alkyl optionally substituted with 1, 2, or 3
 halogen; or OH; or

Y is -N(Y_1)(Y_2); wherein

Y_1 and Y_2 are independently H or C_1 - C_4 alkyl.

More preferred compounds of formula X-XXVIII include those

15 of formula X-XXIX:



X-XXIX.

Preferred compounds of formulas X-XXVIII and X-XXIX

20 include those wherein

N_6 is 0, 1, or 2;

R_{4-1} is selected from the group consisting of - SO_2 -(C_1 - C_8 alkyl),
 - SO_2 - $NR_{4-2}R_{4-3}$; -CO- $NR_{4-3}R_{4-4}$;

R_{4-2} and R_{4-3} are independently H, or C_1 - C_3 alkyl;

25 R_{4-4} is C_1 - C_4 alkyl, phenyl C_1 - C_4 alkyl, C_2 - C_4 alkanoyl, or phenyl
 C_1 - C_4 alkanoyl;

Other preferred compounds of formulas X-XXVIII and X-XXIX
 include those wherein

R₂₀ and A₂ are both hydrogen; and
A₃ and A₄ are independently halogen.

More preferred compounds of formulas X-XXVIII and (X-
5 XXVIX) include those wherein
A₃ and A₄ are meta to each other. More preferably, A₃ and A₄
are at the 3 and 5 positions of the benzene ring.

Other preferred compounds of formula X include those of
10 formula X-XXX, i.e., compounds of formula X wherein
R₄ is H; C₁-C₄ alkyl-NHC(O)R₅; -(CH₂)₀₋₄R₈; -O-C₁-C₄ alkanoyl; OH;
C₆-C₁₀ aryloxy optionally substituted with 1, 2, or 3
groups that are independently halogen, C₁-C₄ alkyl, CO₂H, -
C(O)-C₁-C₄ alkoxy, or C₁-C₄ alkoxy; C₁-C₆ alkoxy; aryl C₁-C₄
15 alkoxy; -C₁-C₄ alkyl-NR₅₀CO₂R₅₁; -C≡N; -CF₃; -CF₂-CF₃; -C≡CH;
-CH₂-CH=CH₂; -(CH₂)₁₋₄-R₄₋₁; -(CH₂)₁₋₄-NH-R₄₋₁; -O-(CH₂)_{n6}-R₄₋₁; -
S-(CH₂)_{n6}-R₄₋₁; (CH₂)₀₋₄-NHC(O)-(CH₂)₀₋₆-R₅₂; or -(CH₂)₀₋₄-R₅₃-
(CH₂)₀₋₄-R₅₄.

20 Preferred compounds of formula X-XXX include those wherein
R₁ is (CH₂)_{n1}-(R_{1-aryl}) where n₁ is zero or one and R_{1-aryl} is
phenyl optionally substituted with 1, 2, 3, or 4 groups
independently selected from C₁-C₆ alkyl optionally
substituted with 1, 2, or 3 substituents selected from the
25 group consisting of C₁-C₃ alkyl, halogen, -OH, -SH,
-NR_{1-a}R_{1-b}, -C≡N, -CF₃, and C₁-C₃ alkoxy; halogen; C₁-C₆
alkoxy; -NR_{N-2}R_{N-3}; and OH; wherein
R_{N-2} and R_{N-3} at each occurrence are independently selected
from the group consisting of -C₁-C₈ alkyl optionally
30 substituted with 1, 2, or 3 groups independently
selected from the group consisting of -OH, -NH₂,
phenyl and halogen; -C₃-C₈ cycloalkyl; -(C₁-C₂ alkyl)-
(C₃-C₈ cycloalkyl); -(C₁-C₆ alkyl)-O-(C₁-C₃ alkyl); -
C₂-C₆ alkenyl; -C₂-C₆ alkynyl; -C₁-C₆ alkyl chain with

one double bond and one triple bond; aryl;
heteroaryl; heterocycloalkyl;

or

5 R_{N-2} , R_{N-3} and the nitrogen to which they are attached form
a 5, 6, or 7 membered heterocycloalkyl or heteroaryl
group, wherein said heterocycloalkyl or heteroaryl
group is optionally fused to a benzene, pyridine, or
pyrimidine ring, and said groups are unsubstituted or
substituted with 1, 2, 3, 4, or 5 groups that at each
10 occurrence are independently C_1 - C_6 alkyl, C_1 - C_6
alkoxy, halogen, halo C_1 - C_6 alkyl, halo C_1 - C_6 alkoxy,
-CN, -NO₂, -NH₂, NH(C_1 - C_6 alkyl), N(C_1 - C_6 alkyl)(C_1 - C_6
alkyl), -OH, -C(O)NH₂, -C(O)NH(C_1 - C_6 alkyl),
-C(O)N(C_1 - C_6 alkyl)(C_1 - C_6 alkyl), C_1 - C_6 alkoxy C_1 - C_6
15 alkyl, C_1 - C_6 thioalkoxy, and C_1 - C_6 thioalkoxy C_1 - C_6
alkyl.

More preferred compounds of formula X-XXX include those
wherein

20 R_2 and R_3 are independently selected from H or C_1 - C_6 alkyl
optionally substituted with 1, 2, or 3 substituents
selected from the group consisting of C_1 - C_3 alkyl,
halogen, -OH, -SH, -C≡N, -CF₃, C_1 - C_3 alkoxy, and -NR_{1-a}R_{1-b};
and
25 R_C is selected from the group consisting of C_1 - C_{10} alkyl
optionally substituted with 1, 2, or 3 groups
independently selected from the group consisting of R_{205} ,
-OC=ONR₂₃₅R₂₄₀, -S(=O)₀₋₂(C_1 - C_6 alkyl), -SH, -NR₂₃₅C=ONR₂₃₅R₂₄₀,
-C=ONR₂₃₅R₂₄₀, and -S(=O)₂NR₂₃₅R₂₄₀; -(CH₂)₀₋₃-(C_3 - C_8)
30 cycloalkyl wherein the cycloalkyl is optionally
substituted with 1, 2, or 3 groups independently selected
from the group consisting of R_{205} , -CO₂H, and -CO₂-(C_1 - C_4
alkyl); -(CR₂₄₅R₂₅₀)₀₋₄-aryl; -(CR₂₄₅R₂₅₀)₀₋₄-heteroaryl; -
(CR₂₄₅R₂₅₀)₀₋₄-heterocycloalkyl; -[C(R₂₅₅)(R₂₆₀)]₁₋₃-CO-N-

(R₂₅₅)₂; -CH(aryl)₂; -CH(heteroaryl)₂;
-CH(heterocycloalkyl)₂; -CH(aryl)(heteroaryl); -CO-
NR₂₃₅R₂₄₀; -(CH₂)₀₋₁-CH((CH₂)₀₋₆-OH)-(CH₂)₀₋₁-aryl; -(CH₂)₀₋₁-
CHR_{C-6}-(CH₂)₀₋₁-heteroaryl; -CH(-aryl or -heteroaryl)-CO-
5 O(C₁-C₄ alkyl); -CH(-CH₂-OH)-CH(OH)-phenyl-NO₂; (C₁-C₆
alkyl)-O-(C₁-C₆ alkyl)-OH; -CH₂-NH-CH₂-CH(-O-CH₂-CH₃)₂; -H;
and -(CH₂)₀₋₆-C(=NR₂₃₅)(NR₂₃₅R₂₄₀); wherein
each aryl is optionally substituted with 1, 2, or 3 R₂₀₀;
each heteroaryl is optionally substituted with 1, 2, 3, or
10 4 R₂₀₀;
each heterocycloalkyl is optionally substituted with 1, 2,
3, or 4 R₂₁₀;
R₂₀₀ at each occurrence is independently selected from the
group consisting of C₁-C₆ alkyl optionally
15 substituted with 1, 2, or 3 R₂₀₅ groups; OH; -NO₂;
halogen; -CO₂H; C≡N; -(CH₂)₀₋₄-CO-NR₂₂₀R₂₂₅; -(CH₂)₀₋₄-CO-
(C₁-C₁₂ alkyl); -(CH₂)₀₋₄-CO₂R₂₁₅; and -(CH₂)₀₋₄-O-(C₁-C₆
alkyl optionally substituted with 1, 2, 3, or 5 -F);
wherein each aryl group at each occurrence is
20 optionally substituted with 1, 2, or 3 groups
that are independently R₂₀₅, R₂₁₀ or C₁-C₆ alkyl
substituted with 1, 2, or 3 groups that are
independently R₂₀₅ or R₂₁₀;
wherein each heterocycloalkyl group at each
25 occurrence is optionally substituted with 1, 2,
or 3 groups that are independently R₂₁₀;
wherein each heteroaryl group at each occurrence is
optionally substituted with 1, 2, or 3 groups
that are independently R₂₀₅, R₂₁₀, or C₁-C₆ alkyl
30 substituted with 1, 2, or 3 groups that are
independently R₂₀₅ or R₂₁₀;
R₂₀₅ at each occurrence is independently selected from the
group consisting of C₁-C₆ alkyl, halogen, -OH, -O-

phenyl, -SH, -C≡N, -CF₃, C₁-C₆ alkoxy, NH₂, NH(C₁-C₆ alkyl), and N-(C₁-C₆ alkyl)(C₁-C₆ alkyl);

5 R₂₁₀ at each occurrence is independently selected from the group consisting of C₁-C₆ alkyl optionally substituted with 1, 2, or 3 R₂₀₅ groups; halogen; C₁-C₆ alkoxy; C₁-C₆ haloalkoxy; -NR₂₂₀R₂₂₅; OH; C≡N; C₃-C₇ cycloalkyl optionally substituted with 1, 2, or 3 R₂₀₅ groups; -CO-(C₁-C₄ alkyl); -SO₂-NR₂₃₅R₂₄₀; -CO-NR₂₃₅R₂₄₀; -SO₂-(C₁-C₄ alkyl); and =O; wherein

10 R₂₁₅ at each occurrence is independently selected from the group consisting of C₁-C₆ alkyl, -(CH₂)₀₋₂-(aryl), C₃-C₇ cycloalkyl, and -(CH₂)₀₋₂-(heteroaryl), -(CH₂)₀₋₂-(heterocycloalkyl); wherein the aryl group at each occurrence is optionally substituted with 1, 2, or 3 groups that are independently R₂₀₅ or R₂₁₀; wherein the heterocycloalkyl group at each occurrence is optionally substituted with 1, 2, or 3 R₂₁₀; wherein each heteroaryl group at each occurrence is optionally substituted with 1, 2, or 3 R₂₁₀;

20 R₂₂₀ and R₂₂₅ at each occurrence are independently selected from the group consisting of -H, -C₁-C₆ alkyl, hydroxy C₁-C₆ alkyl, amino C₁-C₆ alkyl; halo C₁-C₆ alkyl; -C₃-C₇ cycloalkyl, -(C₁-C₆ alkyl)-O-(C₁-C₃ alkyl), -aryl, -heteroaryl, and -heterocycloalkyl; wherein the aryl group at each occurrence is optionally substituted with 1, 2, or 3 R₂₇₀ groups, each heteroaryl is optionally substituted with 1, 2, 3, or 4 R₂₀₀, each heterocycloalkyl is optionally substituted with 1, 2, 3, or 4 R₂₁₀ wherein

30 R₂₇₀ at each occurrence is independently R₂₀₅, C₁-C₆ alkyl optionally substituted with 1, 2, or 3 R₂₀₅ groups; halogen; C₁-C₆ alkoxy; C₁-C₆ haloalkoxy; NR₂₃₅R₂₄₀; OH; C≡N; -CO-(C₁-C₄ alkyl); and =O; wherein the heterocycloalkyl group at each occurrence is

optionally substituted with 1, 2, or 3 R_{205} groups;
wherein each heteroaryl group at each occurrence is
optionally substituted with 1, 2, or 3 R_{205} groups;
 R_{235} and R_{240} at each occurrence are independently H, or C_1 -
5 C_6 alkyl;
 R_{245} and R_{250} at each occurrence are independently selected
from the group consisting of H, C_1 - C_4 alkyl, C_1 - C_4
hydroxyalkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy, or
 R_{245} and R_{250} are taken together with the carbon to which
10 they are attached to form a carbocycle of 3, 4, 5, 6,
or 7 carbon atoms,
 R_{255} and R_{260} at each occurrence are independently selected
from the group consisting of H; C_1 - C_6 alkyl
optionally substituted with 1, 2, or 3 R_{205} groups;
15 $-(CH_2)_{0-4}$ - C_3 - C_7 cycloalkyl optionally substituted with
1, 2, or 3 R_{205} groups; $-(C_1$ - C_4 alkyl)-aryl; $-(C_1$ - C_4
alkyl)-heteroaryl; $-(C_1$ - C_4 alkyl)-heterocycloalkyl; -
aryl; -heteroaryl; -heterocycloalkyl; $-(CH_2)_{1-4}$ - R_{265} -
 $(CH_2)_{0-4}$ -aryl; $-(CH_2)_{1-4}$ - R_{265} - $(CH_2)_{0-4}$ -heteroaryl; and;
20 $-(CH_2)_{1-4}$ - R_{265} - $(CH_2)_{0-4}$ -heterocycloalkyl; wherein
 R_{265} at each occurrence is independently -O-, -S- or -
 $N(C_1$ - C_6 alkyl)-;
each aryl or phenyl is optionally substituted with 1,
2, or 3 groups that are independently R_{205} , R_{210} ,
25 or C_1 - C_6 alkyl substituted with 1, 2, or 3
groups that are independently R_{205} or R_{210} .

Even more preferred compounds of formula X-XXX include
those wherein

30 R_{20} at each occurrence is independently selected from hydrogen,
 C_1 - C_6 alkyl, C_1 - C_4 alkoxy C_1 - C_4 alkyl, halo C_1 - C_6 alkyl, C_2 -
 C_4 alkanoyl, each of which is unsubstituted or substituted
with 1, or 2 groups independently selected from halogen,

C₁-C₆ alkyl, hydroxy, C₁-C₆ alkoxy, NH₂, and -R₂₆-R₂₇,

wherein

R₂₆ is selected from -C(O)-, -SO₂-, -CO₂-;

R₂₇ is selected from C₁-C₆ alkyl, C₁-C₆ alkoxy, aryl C₁-C₆

5 alkyl, piperidyl, pyrrolyl, and pyridyl, wherein each
of the above is unsubstituted or substituted with 1,
2, 3, 4, or 5 groups that are independently C₁-C₄
alkyl, C₁-C₄ alkoxy, halogen, halo C₁-C₆ alkyl,
hydroxy C₁-C₆ alkyl, -C(O)NH₂, NH₂, NH(C₁-C₆ alkyl),
10 N(C₁-C₆ alkyl)(C₁-C₆ alkyl), -C(O)NH(C₁-C₆ alkyl), or -
C(O)N(C₁-C₆ alkyl)(C₁-C₆ alkyl).

Preferred compounds of formula X-XXX include those of
formula X-XXXI, i.e., compounds of formula X-XXX wherein

15 R₄ is H; C₁-C₄ alkyl-NHC(O)R₅; -(CH₂)₀₋₄R₈; -C₁-C₄ alkyl-NR₅₀CO₂R₅₁;
-C≡N; -CF₃; -CF₂-CF₃; -C≡CH; -CH₂-CH=CH₂; -(CH₂)₁₋₄-R₄₋₁; -
(CH₂)₁₋₄-NH-R₄₋₁; (CH₂)₀₋₄-NHC(O)-(CH₂)₀₋₆-R₅₂; or -(CH₂)₀₋₄-R₅₃-
(CH₂)₀₋₄-R₅₄.

20 Preferred compounds of formula X-XXXI include those
wherein

X is C₁-C₄ alkylidenyl optionally optionally substituted with
1, 2, or 3 methyl groups; or -NR₄₋₆-; or

R₄ and R₄₋₆ combine to form -(CH₂)_{n10}-, wherein

25 n₁₀ is 1, 2, 3, or 4;

Z is selected from a bond; SO₂; SO; S; and C(O);

Y is selected from H; C₁-C₄ haloalkyl; C₅-C₆ heterocycloalkyl
containing at least one N, O, or S; phenyl; OH; -

30 N(Y₁)(Y₂); C₁-C₁₀ alkyl optionally substituted with 1 thru
3 substituents which can be the same or different and are
selected from halogen, hydroxy, alkoxy, thioalkoxy, and
haloalkoxy; C₃-C₈ cycloalkyl optionally substituted with
1, 2, or 3 groups independently selected from C₁-C₃ alkyl,
and halogen; alkoxy; phenyl optionally substituted with

halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, CN or NO₂; phenyl C₁-C₄ alkyl optionally substituted with halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, CN or NO₂; wherein

Y₁ and Y₂ are the same or different and are H; C₁-C₁₀ alkyl

5 optionally substituted with 1, 2, or 3 substituents selected from the group consisting of halogen, C₁-C₄ alkoxy, C₃-C₈ cycloalkyl, and OH; C₂-C₆ alkenyl; C₂-C₆ alkanoyl; phenyl; -SO₂-C₁-C₄ alkyl; phenyl C₁-C₄ alkyl; and C₃-C₈ cycloalkyl C₁-C₄ alkyl; or

10 -N(Y₁)(Y₂) forms a ring selected from piperazinyl, piperidinyl, morpholinyl, and pyrrolidinyl, wherein each ring is optionally substituted with 1, 2, 3, or 4 groups that are independently C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkoxy C₁-C₆ alkyl, or halogen.

15

More preferred compounds of formula X-XXXI include those wherein

R₂₀ at each occurrence is independently selected from hydrogen, C₁-C₆ alkyl, C₁-C₄ alkoxy C₁-C₄ alkyl, C₂-C₄ alkanoyl, tertiary-butoxy carbonyl, and benzyloxycarbonyl;

20

R₁ is benzyl which is optionally substituted with 1, 2, 3, or 4 groups independently selected from halogen, C₁-C₄ alkoxy, hydroxy, and C₁-C₄ alkyl optionally substituted with 1, 2, or 3 substituents halogen, OH, SH, NH₂, NH(C₁-C₆ alkyl),

25

N-(C₁-C₆ alkyl)(C₁-C₆ alkyl), C≡N, CF₃;

R₂ and R₃ are independently selected from H or C₁-C₄ alkyl optionally substituted with 1 substituent selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, NH₂, NH(C₁-C₆ alkyl), and NH(C₁-C₆ alkyl)(C₁-C₆ alkyl);

30

R₂₀ at each occurrence is independently hydrogen, C₁-C₆ alkyl, C₁-C₂ alkoxy C₁-C₄ alkyl, halo C₁-C₄ alkyl, C₂-C₆ alkanoyl, each of which is unsubstituted or substituted with 1 or 2 groups independently selected from halogen, hydroxy, and NH₂;

R_C is C_1 - C_8 alkyl optionally substituted with 1, 2, or 3 groups independently selected from R_{205} , -SH, $-C=ONR_{235}R_{240}$, and $-S(=O)_2NR_{235}R_{240}$; $-(CH_2)_{0-3}-(C_3-C_6)$ cycloalkyl wherein the cycloalkyl is optionally substituted with 1, 2, or 3 groups independently selected from R_{205} , $-CO_2H$, and $-CO_2-(C_1-C_4)$ alkyl); $-(CR_{245}R_{250})_{0-4}$ -phenyl optionally substituted with 1, 2, or 3 R_{200} ; $-(CR_{245}R_{250})_{0-3}$ -pyridyl; $-(CR_{245}R_{250})_{0-3}$ -pyridazinyl; $-(CR_{245}R_{250})_{0-3}$ -pyrimidinyl; $-(CR_{245}R_{250})_{0-3}$ -pyrazinyl; $-(CR_{245}R_{250})_{0-3}$ -furyl; $-(CR_{245}R_{250})_{0-3}$ -indolyl; $-(CR_{245}R_{250})_{0-3}$ -thienyl; $-(CR_{245}R_{250})_{0-3}$ -pyrrolyl; $-(CR_{245}R_{250})_{0-3}$ -pyrazolyl; $(CR_{245}R_{250})_{0-3}$ -benzoxazolyl; $-(CR_{245}R_{250})_{0-3}$ -imidazolyl; each of the above heteroaryl groups is optionally substituted with 1, 2, 3, or 4 R_{200} ; $-(CR_{245}R_{250})_{0-3}$ -imidazolidinyl; $(CR_{245}R_{250})_{0-3}$ -tetrahydrofuryl; $(CR_{245}R_{250})_{0-3}$ -tetrahydropyranyl; $(CR_{245}R_{250})_{0-3}$ -piperazinyl; $(CR_{245}R_{250})_{0-3}$ -pyrrolidinyl; $(CR_{245}R_{250})_{0-3}$ -piperidinyl; $(CR_{245}R_{250})_{0-3}$ -indolinyl; each of the above heterocycloalkyl groups is optionally substituted with 1, 2, 3, or 4 R_{210} ; $(CH_2)_{0-1}-CH((CH_2)_{0-4}-OH)-(CH_2)_{0-1}$ -phenyl; $-(CH_2)_{0-1}-CH(C_1-C_4$ hydroxyalkyl) $-(CH_2)_{0-1}$ -pyridyl;

R_{200} at each occurrence is independently C_1 - C_6 alkyl optionally substituted with 1, 2, or 3 R_{205} groups; OH; $-NO_2$; halogen; $-CO_2H$; $C\equiv N$; $-(CH_2)_{0-4}-CO-NR_{220}R_{225}$; $-(CH_2)_{0-4}-CO-(C_1-C_8)$ alkyl); $-(CH_2)_{0-4}-CO_2R_{215}$; and $-(CH_2)_{0-4}-O-(C_1-C_6)$ alkyl optionally substituted with 1, 2, 3, or 5 -F);

R_{205} at each occurrence is independently C_1 - C_6 alkyl, halogen, -OH, -O-phenyl, -SH, $-C\equiv N$, $-CF_3$, C_1 - C_6 alkoxy, NH_2 , $NH(C_1-C_6)$ alkyl), and $N-(C_1-C_6)$ alkyl)(C_1-C_6 alkyl);

R_{210} at each occurrence is independently C_1 - C_6 alkyl optionally substituted with 1 or 2 R_{205} groups; halogen; C_1 - C_4 alkoxy; C_1 - C_4 haloalkoxy; $-NR_{220}R_{225}$; OH; $C\equiv N$; C_3 - C_7 cycloalkyl optionally substituted with 1

or 2 R_{205} groups; $-\text{CO}-(\text{C}_1-\text{C}_4 \text{ alkyl})$; $-\text{SO}_2-\text{NR}_{235}\text{R}_{240}$; $-\text{CO}-\text{NR}_{235}\text{R}_{240}$; $-\text{SO}_2-(\text{C}_1-\text{C}_4 \text{ alkyl})$; and $=\text{O}$; wherein

R_{215} at each occurrence is independently C_1-C_6 alkyl, $-(\text{CH}_2)_{0-2}-(\text{phenyl})$, C_3-C_6 cycloalkyl, $-(\text{CH}_2)_{0-2}-(\text{pyridyl})$, $-(\text{CH}_2)_{0-2}-(\text{pyrrolyl})$, $-(\text{CH}_2)_{0-2}-(\text{imidazolyl})$, $-(\text{CH}_2)_{0-2}-(\text{pyrimidyl})$, $-(\text{CH}_2)_{0-2}-(\text{pyrrolidinyl})$, $-(\text{CH}_2)_{0-2}-(\text{imidazolidinyl})$, $-(\text{CH}_2)_{0-2}-(\text{piperazinyl})$, $-(\text{CH}_2)_{0-2}-(\text{piperidinyl})$, and $-(\text{CH}_2)_{0-2}-(\text{morpholinyl})$; wherein the phenyl group at each occurrence is optionally substituted with 1 or 2 groups that are independently R_{205} or R_{210} ; wherein each heterocycloalkyl group at each occurrence is optionally substituted with 1 or 2 R_{210} ; wherein each heteroaryl group at each occurrence is optionally substituted with 1 or 2 R_{210} ;

R_{220} and R_{225} at each occurrence are independently $-\text{H}$, $-\text{C}_1-\text{C}_4$ alkyl, hydroxy C_1-C_4 alkyl, halo C_1-C_4 alkyl; $-\text{C}_3-\text{C}_6$ cycloalkyl, and $-(\text{C}_1-\text{C}_4 \text{ alkyl})-\text{O}-(\text{C}_1-\text{C}_2 \text{ alkyl})$;

R_{235} and R_{240} at each occurrence are independently H , or C_1-C_6 alkyl;

R_{245} and R_{250} at each occurrence are independently H , C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, or

R_{245} and R_{250} are taken together with the carbon to which they are attached to form a carbocycle of 3, 5, or 6 carbon atoms.

Even more preferred compounds of formula X-XXXI include those wherein

R_4 is H ; C_1-C_4 alkyl- $\text{NHC}(\text{O})\text{R}_5$; $-(\text{CH}_2)_{0-4}\text{R}_8$; $-\text{C}_1-\text{C}_4$ alkyl- $\text{NR}_{50}\text{CO}_2\text{R}_{51}$; $-(\text{CH}_2)_{1-4}-\text{R}_{4-1}$; $-(\text{CH}_2)_{1-4}-\text{NH}-\text{R}_{4-1}$; $(\text{CH}_2)_{1-4}-\text{NHC}(\text{O})-(\text{CH}_2)_{0-6}-\text{R}_{52}$; or $-(\text{CH}_2)_{1-4}-\text{R}_{53}-(\text{CH}_2)_{0-4}-\text{R}_{54}$; wherein R_{4-1} is $-\text{SO}_2-(\text{C}_1-\text{C}_8 \text{ alkyl})$, $-\text{SO}_2-\text{NR}_{4-2}\text{R}_{4-3}$; or $-\text{CO}-\text{NR}_{4-3}\text{R}_{4-4}$; wherein

R₄₋₂ and R₄₋₃ are independently H, or C₁-C₃ alkyl;

R₄₋₄ is C₁-C₄ alkyl, phenyl C₁-C₄ alkyl, C₂-C₄ alkanoyl, or phenyl C₁-C₄ alkanoyl;

R₅ is selected from the group consisting of cyclopropyl;

cyclopentyl; cyclohexyl; C₁-C₆ alkyl optionally

substituted with 1, 2, or 3 groups that are

independently halogen, -NR₆R₇, C₁-C₄ alkoxy, C₅-C₆

heterocycloalkyl, C₅-C₆ heteroaryl, phenyl, C₃-C₇

cycloalkyl, -S-C₁-C₄ alkyl, -SO₂-C₁-C₄ alkyl, -CO₂H,

-CONR₆R₇, -CO₂-C₁-C₄ alkyl, or phenyloxy; pyridyl,

thiazolyl, pyrazolyl, pyrazinyl, optionally

substituted with 1, 2, or 3 groups that are

independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, C₁-C₄

haloalkyl, or OH; piperidinyl, dihydropyridazinonyl,

pyrrolidinonyl, thioxothiazolidinonyl, isoxazolyl,

imidazolyl, indolyl, optionally substituted with 1,

2, or 3 groups that are independently C₁-C₄ alkyl, C₁-

C₄ alkoxy, halogen, or C₂-C₄ alkanoyl; phenyl

optionally substituted with 1, 2, 3, or 4 groups that

are independently halogen, OH, C₁-C₄ alkyl, C₁-C₄

alkoxy, or C₁-C₄ haloalkyl; wherein

R₆ and R₇ are independently selected from the group

consisting of H, C₁-C₆ alkyl, C₂-C₆ alkanoyl, phenyl,

-SO₂-C₁-C₄ alkyl, benzyl, and phenethyl;

R₈ is -SO₂-thienyl optionally substituted with 1 or 2

groups that are independently C₁-C₄ alkyl or halogen;

-SO₂-phenyl, -SO₂-piperidinyl, -SO₂-pyrrolidinyl,

imidazolidinyyl dione, -C(O)NHR₉, -S-C₁-C₆ alkyl, or -

S-C₂-C₄ alkanoyl, wherein

R₉ is phenyl C₁-C₄ alkyl, C₁-C₄ alkyl, or H;

R₅₀ is H or C₁-C₄ alkyl;

R₅₁ is selected from benzyl; phenethyl; C₁-C₆ alkyl

optionally substituted with 1, 2, or 3 groups that

are independently halogen, cyano, -NR₆R₇, -C(O)NR₆R₇,

or -C₁-C₄ alkoxy; heterocycloalkyl containing at least one N, O, or S and optionally substituted with 1 or 2 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, C₂-C₄ alkanoyl, phenyl C₁-C₄ alkyl, and -SO₂ C₁-C₄ alkyl; heterocycloalkylalkyl containing at least one N, O, or S and optionally substituted with 1 or 2 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, C₂-C₄ alkanoyl, phenyl C₁-C₄ alkyl, and -SO₂ C₁-C₄ alkyl; C₂-C₆ alkenyl; C₂-C₆ alkynyl; heteroaryl optionally substituted with 1, 2, or 3 groups that are independently OH, C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, NH₂, NH(C₁-C₆ alkyl) or N(C₁-C₆ alkyl)(C₁-C₆ alkyl); heteroarylalkyl containing at least one N, O, or S and optionally substituted with 1, 2, or 3 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, NH₂, NH(C₁-C₆ alkyl) or N(C₁-C₆ alkyl)(C₁-C₆ alkyl); phenyl; C₃-C₆ cycloalkyl, and C₃-C₆ cycloalkyl C₁-C₄ alkyl, wherein the phenyl; C₃-C₆ cycloalkyl, and C₃-C₆ cycloalkyl C₁-C₄ alkyl groups are optionally substituted with 1, 2, or 3 groups that are independently halogen, CN, NO₂, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₂-C₆ alkanoyl, C₁-C₄ haloalkyl, C₁-C₄ haloalkoxy, hydroxy, C₁-C₄ hydroxyalkyl, C₁-C₄ thioalkoxy;

R₅₂ is heterocycloalkyl, heteroaryl, phenyl, C₃-C₆ cycloalkyl, -S(O)₀₋₂-C₁-C₆ alkyl, CO₂H, -C(O)NH₂, -C(O)NH(alkyl), -C(O)N(alkyl)(alkyl), -CO₂-alkyl, -NHS(O)₀₋₂-C₁-C₆ alkyl, -N(alkyl)S(O)₀₋₂-C₁-C₆ alkyl, -S(O)₀₋₂-heteroaryl, -S(O)₀₋₂-aryl, -NH(arylalkyl), -N(alkyl)(arylalkyl), thioalkoxy, or alkoxy, each of which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ thioalkoxy, halogen, C₁-C₄ haloalkyl,

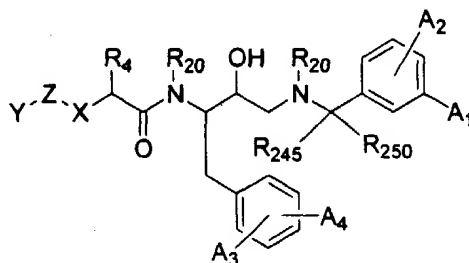
haloalkoxy, C₂-C₆ alkanoyl, NO₂, CN, C₁-C₄

alkoxycarbonyl, or aminocarbonyl;

R₅₃ is absent, -O-, -C(O)-, -NH-, -N(alkyl)-, -NH-S(O)₀₋₂-,
-N(alkyl)-S(O)₀₋₂-, -S(O)₀₋₂-NH-, or -S(O)₀₋₂-N(alkyl)-;

5 R₅₄ is pyridyl, thienyl, imidazolyl, phenyl, phenyl C₁-C₄
alkyl, piperidyl, pyrrolidinyl, imidazolidinyl dione,
CO₂H, -CO₂-alkyl, -C(O)NH(alkyl), -C(O)N(alkyl)
(alkyl), -C(O)NH₂, C₁-C₈ alkyl, OH, phenyloxy, alkoxy,
phenylalkoxy, NH₂, NH(alkyl), N(alkyl) (alkyl), or -
10 C₁-C₆ alkyl-CO₂-C₁-C₆ alkyl, each of which is
optionally substituted with 1, 2, 3, 4, or 5 groups
that are independently alkyl, alkoxy, CO₂H, -CO₂-
alkyl, thioalkoxy, halogen, haloalkyl, haloalkoxy,
hydroxyalkyl, alkanoyl, NO₂, CN, alkoxycarbonyl, or
15 aminocarbonyl.

Even more preferred compounds of formula X-XXXI are those
of formula X-XXXII:



X-XXXII

wherein

A₁ is H, C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen or C₂-C₆ alkynyl;

A₂ is H, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, C₁-C₄

25 haloalkyl or OH;

A₃ and A₄ are independently C₁-C₄ alkyl, halogen, or H.

Preferred compounds of formulas X-XXXI and X-XXXII include
those wherein

R_{20} at each occurrence is independently H or C_1 - C_4 alkyl;

X is C_1 or C_2 alkylidenyl;

Z is SO_2 ; SO; S; or C(O); and

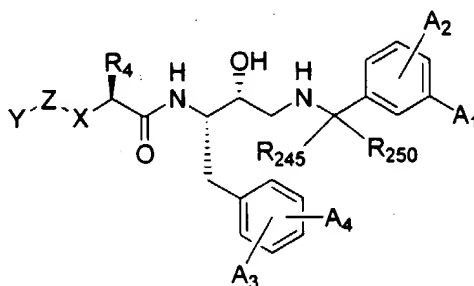
Y is phenyl; C_1 - C_{10} alkyl optionally substituted with 1, 2, or 3

5 halogen; or OH; or

Y is $-N(Y_1)(Y_2)$; wherein

Y_1 and Y_2 are independently H or C_1 - C_4 alkyl.

10 More preferred compounds of formula X-XXXII include those of formula X-XXXIII:



X-XXXIII.

15 Preferred compounds of formulas X-XXXII and X-XXXIII include those wherein

R_4 is H; or C_1 - C_4 alkyl-NHC(O) R_5 ; wherein

R_5 is selected from the group consisting of cyclopropyl;

cyclopentyl; cyclohexyl; C_1 - C_6 alkyl optionally substituted with 1, 2, or 3 groups that are independently
 20 halogen, $-NR_6R_7$, C_1 - C_4 alkoxy, C_5 - C_6 heterocycloalkyl, C_5 - C_6 heteroaryl, phenyl, C_3 - C_7 cycloalkyl, $-S-C_1$ - C_4 alkyl, $-SO_2$ - C_1 - C_4 alkyl, $-CO_2H$, $-CONR_6R_7$, $-CO_2$ - C_1 - C_4 alkyl, or phenyloxy; pyridyl, thiazolyl, pyrazolyl, pyrazinyl, optionally substituted with 1, 2, or 3 groups that are
 25 independently C_1 - C_4 alkyl, C_1 - C_4 alkoxy, halogen, C_1 - C_4 haloalkyl, or OH; piperidinyl, dihydropyridazinonyl, pyrrolidinonyl, thioxothiazolidinonyl, isoxazolyl, imidazolyl, indolyl, optionally substituted with 1, 2, or 3 groups that are independently C_1 - C_4 alkyl, C_1 - C_4 alkoxy,

halogen, or C₂-C₄ alkanoyl; phenyl optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, OH, C₁-C₄ alkyl, C₁-C₄ alkoxy, or C₁-C₄ haloalkyl; wherein R₆ and R₇ are independently selected from the group

- 5 consisting of H, C₁-C₆ alkyl, C₂-C₆ alkanoyl, phenyl, -SO₂-C₁-C₄ alkyl, benzyl, and phenethyl.

Other preferred compounds of formula X-XXXIII include those wherein

- 10 R₄ is -(CH₂)₀₋₄R₈; wherein

R₈ is -SO₂-thienyl optionally substituted with 1 or 2 groups that are independently C₁-C₄ alkyl or halogen; -SO₂-phenyl, -SO₂-piperidinyl, -SO₂-pyrrolidinyl, imidazolidinyyl dione, -C(O)NHR₉, -S-C₁-C₆ alkyl, or -S-C₂-C₄ alkanoyl, wherein

- 15 R₉ is phenyl C₁-C₄ alkyl, C₁-C₄ alkyl, or H;

Other preferred compounds of formula X-XXXIII include those wherein

- 20 R₄ is -C₁-C₄ alkyl-NR₅₀CO₂R₅₁; -(CH₂)₁₋₄-NH-R₄₋₁; or (CH₂)₁₋₄-NHC(O)-(CH₂)₀₋₆-R₅₂; wherein

R₅₀ is H or C₁-C₄ alkyl;

R₅₁ is selected from benzyl; phenethyl; C₁-C₆ alkyl

- 25 optionally substituted with 1, 2, or 3 groups that are independently halogen, cyano, -NR₆R₇, -C(O)NR₆R₇, or -C₁-C₄ alkoxy; heterocycloalkyl containing at least one N, O, or S and optionally substituted with 1 or 2 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, C₂-C₄ alkanoyl, phenyl C₁-C₄ alkyl, and -SO₂ C₁-C₄ alkyl; heterocycloalkylalkyl
- 30 containing at least one N, O, or S and optionally substituted with 1 or 2 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, C₂-C₄ alkanoyl, phenyl C₁-C₄ alkyl, and -SO₂ C₁-C₄ alkyl; C₂-C₆

alkenyl; C₂-C₆ alkynyl; heteroaryl optionally substituted with 1, 2, or 3 groups that are independently OH, C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, NH₂, NH(C₁-C₆ alkyl) or N(C₁-C₆ alkyl)(C₁-C₆ alkyl); heteroarylalkyl containing at least one N, O, or S and optionally substituted with 1, 2, or 3 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, NH₂, NH(C₁-C₆ alkyl) or N(C₁-C₆ alkyl)(C₁-C₆ alkyl); phenyl; C₃-C₆ cycloalkyl, and C₃-C₆ cycloalkyl C₁-C₄ alkyl, wherein the phenyl; C₃-C₆ cycloalkyl, and C₃-C₆ cycloalkyl C₁-C₄ alkyl groups are optionally substituted with 1, 2, or 3 groups that are independently halogen, CN, NO₂, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₂-C₆ alkanoyl, C₁-C₄ haloalkyl, C₁-C₄ haloalkoxy, hydroxy, C₁-C₄ hydroxyalkyl, C₁-C₄ thioalkoxy;

R₆ and R₇ are independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkanoyl, phenyl, -SO₂-C₁-C₄ alkyl, benzyl, and phenethyl;

R₅₂ is heterocycloalkyl, heteroaryl, phenyl, C₃-C₆ cycloalkyl, -S(O)₀₋₂-C₁-C₆ alkyl, CO₂H, -C(O)NH₂, -C(O)NH(alkyl), -C(O)N(alkyl)(alkyl), -CO₂-alkyl, -NHS(O)₀₋₂-C₁-C₆ alkyl, -N(alkyl)S(O)₀₋₂-C₁-C₆ alkyl, -S(O)₀₋₂-heteroaryl, -S(O)₀₋₂-aryl, -NH(arylalkyl), -N(alkyl)(arylalkyl), thioalkoxy, or alkoxy, each of which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ thioalkoxy, halogen, C₁-C₄ haloalkyl, haloalkoxy, C₂-C₆ alkanoyl, NO₂, CN, C₁-C₄ alkoxycarbonyl, or aminocarbonyl.

Still other preferred compounds of formula X-XXXIII include those wherein

R₄ is -(CH₂)₁₋₄-R₄₋₁ or -(CH₂)₁₋₄-R₅₃-(CH₂)₀₋₄-R₅₄; wherein

R_{4-1} is $-\text{SO}_2-(\text{C}_1-\text{C}_8 \text{ alkyl})$, $-\text{SO}_2-\text{NR}_{4-2}\text{R}_{4-3}$; or $-\text{CO}-\text{NR}_{4-3}\text{R}_{4-4}$;

wherein

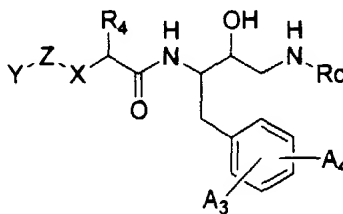
R_{4-2} and R_{4-3} are independently H, or C_1-C_3 alkyl;

R_{4-4} is C_1-C_4 alkyl, phenyl C_1-C_4 alkyl, C_2-C_4 alkanoyl, or phenyl C_1-C_4 alkanoyl;

R_{53} is absent, $-\text{O}-$, $-\text{C}(\text{O})-$, $-\text{NH}-$, $-\text{N}(\text{alkyl})-$, $-\text{NH}-\text{S}(\text{O})_{0-2}-$, $-\text{N}(\text{alkyl})-\text{S}(\text{O})_{0-2}-$, $-\text{S}(\text{O})_{0-2}-\text{NH}-$, or $-\text{S}(\text{O})_{0-2}-\text{N}(\text{alkyl})-$;

R_{54} is pyridyl, thienyl, imidazolyl, phenyl, phenyl C_1-C_4 alkyl, piperidyl, pyrrolidinyl, imidazolidinyl dione, CO_2H , $-\text{CO}_2\text{-alkyl}$, $-\text{C}(\text{O})\text{NH}(\text{alkyl})$, $-\text{C}(\text{O})\text{N}(\text{alkyl})$ (alkyl), $-\text{C}(\text{O})\text{NH}_2$, C_1-C_8 alkyl, OH, phenyloxy, alkoxy, phenylalkoxy, NH_2 , $\text{NH}(\text{alkyl})$, $\text{N}(\text{alkyl})$ (alkyl), or $-\text{C}_1-\text{C}_6$ alkyl- $\text{CO}_2-\text{C}_1-\text{C}_6$ alkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, alkoxy, CO_2H , $-\text{CO}_2\text{-alkyl}$, thioalkoxy, halogen, haloalkyl, haloalkoxy, hydroxyalkyl, alkanoyl, NO_2 , CN, alkoxycarbonyl, or aminocarbonyl.

Other preferred compounds of formula X-XXXIII include those of formula X-XXXIV:



X-XXXIV

wherein

R_c is C_3-C_8 alkyl, cyclopropyl, cyclopentyl, cyclohexyl, or $(\text{C}_1-\text{C}_4)\text{alkyl}-(\text{C}_3-\text{C}_6)$ cycloalkyl; and

A_3 and A_4 are independently C_1-C_4 alkyl, halogen, or H.

Preferred compounds of formula X-XXXIV include

R_{20} at each occurrence is independently H or C_1-C_4 alkyl;

X is C_1 or C_2 alkylidenyl;

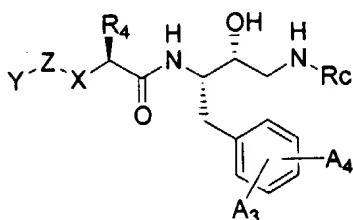
Z is SO₂; SO; S; or C(O); and

Y is phenyl; C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3
halogen; or OH; or

Y is -N(Y₁)(Y₂); wherein

5 Y₁ and Y₂ are independently H or C₁-C₄ alkyl.

More preferred compounds of formula X-XXXIV include those
of formula X-XXXV:



X-XXXV.

Preferred compounds of formula X-XXXV include those
wherein

R₄ is H; or C₁-C₄ alkyl-NHC(O)R₅; wherein

15 R₅ is selected from the group consisting of cyclopropyl;
cyclopentyl; cyclohexyl; C₁-C₆ alkyl optionally
substituted with 1, 2, or 3 groups that are independently
halogen, -NR₆R₇, C₁-C₄ alkoxy, C₅-C₆ heterocycloalkyl, C₅-C₆
heteroaryl, phenyl, C₃-C₇ cycloalkyl, -S-C₁-C₄ alkyl, -SO₂-
20 C₁-C₄ alkyl, -CO₂H, -CONR₆R₇, -CO₂-C₁-C₄ alkyl, or
phenyloxy; pyridyl, thiazolyl, pyrazolyl, pyrazinyl,
optionally substituted with 1, 2, or 3 groups that are
independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, C₁-C₄
haloalkyl, or OH; piperidinyl, dihydropyridazinonyl,
25 pyrrolidinonyl, thioxothiazolidinonyl, isoxazolyl,
imidazolyl, indolyl, optionally substituted with 1, 2, or
3 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy,
halogen, or C₂-C₄ alkanoyl; phenyl optionally substituted
with 1, 2, 3, or 4 groups that are independently halogen,

OH, C₁-C₄ alkyl, C₁-C₄ alkoxy, or C₁-C₄ haloalkyl; and NR₆R₇ wherein

R₆ and R₇ are independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkanoyl, phenyl, -SO₂-C₁-C₄ alkyl, benzyl, and phenethyl.

Other preferred compounds of formula X-XXXV include those wherein

R₄ is -(CH₂)₀₋₄R₈; wherein

- 10 R₈ is -SO₂-thienyl optionally substituted with 1 or 2 groups that are independently C₁-C₄ alkyl or halogen; -SO₂-phenyl, -SO₂-piperidinyl, -SO₂-pyrrolidinyl, imidazolidinyll dione, -C(O)NHR₉, -S-C₁-C₆ alkyl, or -S-C₂-C₄ alkanoyl, wherein
- 15 R₉ is phenyl C₁-C₄ alkyl, C₁-C₄ alkyl, or H;

Other preferred compounds of formula X-XXXV include those wherein

R₄ is -C₁-C₄ alkyl-NR₅₀CO₂R₅₁; -(CH₂)₁₋₄-NH-R₄₋₁; or (CH₂)₁₋₄-NHC(O)-(CH₂)₀₋₆-R₅₂; wherein

- 20 R₅₀ is H or C₁-C₄ alkyl;
- R₅₁ is selected from benzyl; phenethyl; C₁-C₆ alkyl optionally substituted with 1, 2, or 3 groups that are independently halogen, cyano, -NR₆R₇, -C(O)NR₆R₇, or -C₁-C₄ alkoxy; heterocycloalkyl containing at least one N, O, or S and optionally substituted with 1 or 2 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, C₂-C₄ alkanoyl, phenyl C₁-C₄ alkyl, and -SO₂ C₁-C₄ alkyl; heterocycloalkylalkyl containing at least one N, O, or S and optionally substituted with 1 or 2 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, C₂-C₄ alkanoyl, phenyl C₁-C₄ alkyl, and -SO₂ C₁-C₄ alkyl; C₂-C₆ alkenyl; C₂-C₆ alkynyl; heteroaryl optionally
- 25
- 30

substituted with 1, 2, or 3 groups that are
independently OH, C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen,
NH₂, NH(C₁-C₆ alkyl) or N(C₁-C₆ alkyl)(C₁-C₆ alkyl);
heteroarylalkyl containing at least one N, O, or S
and optionally substituted with 1, 2, or 3 groups
that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy,
halogen, NH₂, NH(C₁-C₆ alkyl) or N(C₁-C₆ alkyl)(C₁-C₆
alkyl); phenyl; C₃-C₆ cycloalkyl, and C₃-C₆ cycloalkyl
C₁-C₄ alkyl, wherein the phenyl; C₃-C₆ cycloalkyl, and
C₃-C₆ cycloalkyl C₁-C₄ alkyl groups are optionally
substituted with 1, 2, or 3 groups that are
independently halogen, CN, NO₂, C₁-C₄ alkyl, C₁-C₄
alkoxy, C₂-C₆ alkanoyl, C₁-C₄ haloalkyl, C₁-C₄
haloalkoxy, hydroxy, C₁-C₄ hydroxyalkyl, C₁-C₄
thioalkoxy;

R₆ and R₇ are independently selected from the group
consisting of H, C₁-C₆ alkyl, C₂-C₆ alkanoyl,
phenyl, -SO₂-C₁-C₄ alkyl, benzyl, and phenethyl;

R₅₂ is heterocycloalkyl, heteroaryl, phenyl, C₃-C₆
cycloalkyl, -S(O)₀₋₂-C₁-C₆ alkyl, CO₂H, -C(O)NH₂,
-C(O)NH(alkyl), -C(O)N(alkyl)(alkyl), -CO₂-alkyl,
-NHS(O)₀₋₂-C₁-C₆ alkyl, -N(alkyl)S(O)₀₋₂-C₁-C₆ alkyl,
-S(O)₀₋₂-heteroaryl, -S(O)₀₋₂-aryl, -NH(arylalkyl),
-N(alkyl)(arylalkyl), thioalkoxy, or alkoxy, each of
which is optionally substituted with 1, 2, 3, 4, or 5
groups that are independently C₁-C₄ alkyl, C₁-C₄
alkoxy, C₁-C₄ thioalkoxy, halogen, C₁-C₄ haloalkyl,
haloalkoxy, C₂-C₆ alkanoyl, NO₂, CN, C₁-C₄
alkoxycarbonyl, or aminocarbonyl.

Still other preferred compounds of formula X-XXXV include
those wherein

R₄ is -(CH₂)₁₋₄-R₄₋₁ or -(CH₂)₁₋₄-R₅₃-(CH₂)₀₋₄-R₅₄; wherein

R_{4-1} is $-\text{SO}_2-(\text{C}_1-\text{C}_8 \text{ alkyl})$, $-\text{SO}_2-\text{NR}_{4-2}\text{R}_{4-3}$; or $-\text{CO}-\text{NR}_{4-3}\text{R}_{4-4}$;

wherein

R_{4-2} and R_{4-3} are independently H, or C_1-C_3 alkyl;

R_{4-4} is C_1-C_4 alkyl, phenyl C_1-C_4 alkyl (preferably benzyl of phenethyl), C_2-C_4 alkanoyl, or phenyl C_1-C_4 alkanoyl (preferably benzoyl or $\text{C}_6\text{H}_5\text{CH}_2\text{CO}-$);

R_{53} is absent, $-\text{O}-$, $-\text{C}(\text{O})-$, $-\text{NH}-$, $-\text{N}(\text{alkyl})-$, $-\text{NH}-\text{S}(\text{O})_{0-2}-$, $-\text{N}(\text{alkyl})-\text{S}(\text{O})_{0-2}-$, $-\text{S}(\text{O})_{0-2}-\text{NH}-$, or $-\text{S}(\text{O})_{0-2}-\text{N}(\text{alkyl})-$;

R_{54} is pyridyl, thienyl, imidazolyl, phenyl, phenyl C_1-C_4 alkyl, piperidyl, pyrrolidinyl, imidazolidinyl dione, CO_2H , $-\text{CO}_2\text{-alkyl}$, $-\text{C}(\text{O})\text{NH}(\text{alkyl})$, $-\text{C}(\text{O})\text{N}(\text{alkyl})$ (alkyl), $-\text{C}(\text{O})\text{NH}_2$, C_1-C_8 alkyl, OH, phenyloxy, alkoxy, phenylalkoxy, NH_2 , $\text{NH}(\text{alkyl})$, $\text{N}(\text{alkyl})$ (alkyl), or $-\text{C}_1-\text{C}_6$ alkyl- $\text{CO}_2-\text{C}_1-\text{C}_6$ alkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, alkoxy, CO_2H , $-\text{CO}_2\text{-alkyl}$, thioalkoxy, halogen, haloalkyl, haloalkoxy, hydroxyalkyl, alkanoyl, NO_2 , CN, alkoxycarbonyl, or aminocarbonyl.

Other preferred compounds of formula X-XXXII include those of formula X-XXXVI, i.e., compounds of formula X-XXXII wherein R_4 is $-\text{O}-\text{C}_1-\text{C}_4$ alkanoyl; OH; C_6-C_{10} aryloxy optionally substituted with 1, 2, or 3 groups that are independently halogen, C_1-C_4 alkyl, CO_2H , $-\text{C}(\text{O})-\text{C}_1-\text{C}_4$ alkoxy, or C_1-C_4 alkoxy; C_1-C_6 alkoxy; aryl C_1-C_4 alkoxy; $-\text{O}-(\text{CH}_2)_{n6}-\text{R}_{4-1}$; $-\text{S}-(\text{CH}_2)_{n6}-\text{R}_{4-1}$.

Still other preferred compounds of formula X-XXXVI include those wherein

R_4 is $-\text{O}-\text{C}_1-\text{C}_4$ alkanoyl; OH; phenyloxy or naphthyloxy, each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, C_1-C_4 alkyl, CO_2H , $-\text{C}(\text{O})-$

C₁-C₄ alkoxy, or C₁-C₄ alkoxy; C₁-C₆ alkoxy; phenyl C₁-C₄ alkoxy; -O-(CH₂)_{n6}-R₄₋₁; or -S-(CH₂)_{n6}-R₄₋₁

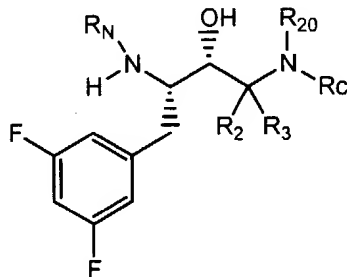
R₄₋₁ is -SO₂-(C₁-C₈ alkyl), -SO₂-NR₄₋₂R₄₋₃; or -CO-NR₄₋₃R₄₋₄; wherein R₄₋₂ and R₄₋₃ are independently H, or C₁-C₃ alkyl;

5 R₄₋₄ is C₁-C₄ alkyl, phenyl C₁-C₄ alkyl, C₂-C₄ alkanoyl, or phenyl C₁-C₄ alkanoyl;

More preferred compounds of formula X-XXXVI include those wherein

10 R₄ is -O-C₁-C₄ alkanoyl; OH; phenyloxy optionally substituted with 1, or 2 groups that are independently halogen, C₁-C₄ alkyl, CO₂H, -C(O)-C₁-C₄ alkoxy, or C₁-C₄ alkoxy; or phenyl C₁-C₄ alkoxy.

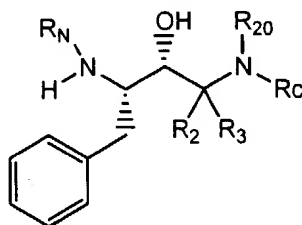
15 Other preferred compounds of the invention are those of formulae X-40 to X-47:



X-40

where R_N, R₂, R₃, R₂₀ and R_C are as defined above for structure

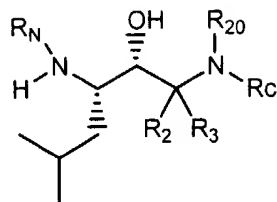
20 X.



X-41

where R_N, R₂, R₃, R₂₀ and R_C are as defined above for structure X.

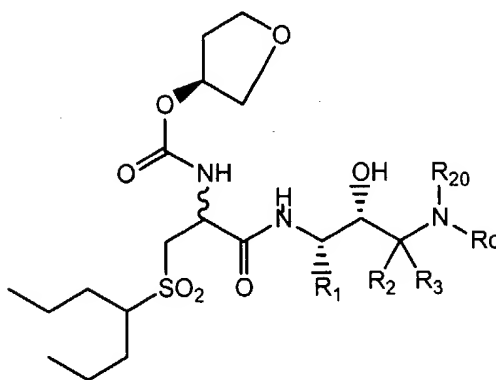
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X-42

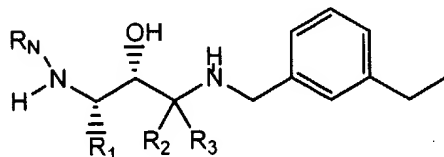
where R_N , R_2 , R_3 , R_{20} and R_c are as defined above for structure X.

5



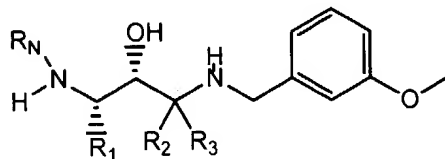
X-43

where R_1 , R_2 , R_3 , R_{20} and R_c are as defined above for structure X.



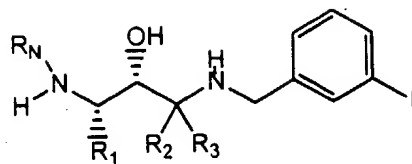
X-44

where R_N , R_1 , R_2 , and R_3 are as defined above for structure X.



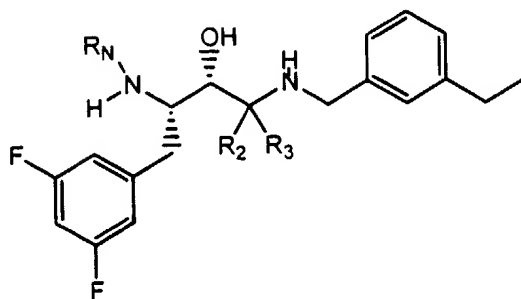
X-45

15 where R_N , R_1 , R_2 , and R_3 are as defined above for structure X.



X-46

where R_N , R_1 , R_2 , and R_3 are as defined above for structure X.



X-47

where R_N , R_2 , and R_3 are as defined above for structure X.

Other representative compounds of the invention are

N-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-3-(ethylthio)-2-[[[(isobutylsulfonyl)amino]methyl]propanamide;

N-1--((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-N-2--(isopentylsulfonyl)-L-methioninamide;

N-2--[(5-chlorothien-2-yl)sulfonyl]-N-1--((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)-2-[[[(1-propylbutyl)sulfonyl]methyl]propanamide;

N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)-2-[[[(1-propylbutyl)sulfonyl]methyl]propanamide;

N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)-2-[[1-propylbutyl)sulfonyl)methyl]propanamide; and

S-{3-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)amino)-2-[(isopentylsulfonyl)methyl]-3-oxopropyl} ethanethioate and the pharmaceutically acceptable salts thereof.

Still other representative compounds of the invention are selected from:

4-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)amino)-4-oxo-3-[[1-propylbutyl)sulfonyl)methyl]butanoic acid;

4-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)amino)-3-[(isopentylsulfonyl)methyl]-4-oxobutanoic acid;

methyl 4-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)amino)-3-[(isopentylsulfonyl)methyl]-4-oxobutanoate;

N-1-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-2-[(isopentylsulfonyl)methyl]succinamide;

N-1-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-2-[(isopentylsulfonyl)methyl]-N-4-methylsuccinamide;

N-1-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-2-[(isopentylsulfonyl)methyl]-N-4,N-4-dimethylsuccinamide;

N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)-2-[[1-propylbutyl)sulfonyl)methyl]propanamide;

N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-

ethylbenzyl)amino]-2-hydroxypropyl}-3-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)-2-[[1-propylbutyl)sulfonyl)methyl]propanamide;

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)-2-[[1-propylbutyl)sulfonyl)methyl]propanamide;

N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-3-(ethylsulfonyl)-2-[[1-(isobutylsulfonyl)amino]methyl]propanamide; and

(2S)-N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-2-[(isopentylsulfonyl)amino]-4-(methylsulfonyl)butanamide and the pharmaceutically acceptable salts thereof.

Yet still other representative compounds of the invention are:

2-N-1-~{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-[(butylsulfonyl)methyl]-2-oxoethyl acetate;

N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-2-hydroxy-3-[(1-propylbutyl)sulfonyl]propanamide;

N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-2-hydroxy-3-(isopentylsulfonyl)propanamide;

N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-2-hydroxy-3-[(3-methoxyphenyl)sulfonyl]propanamide;

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-hydroxy-4-(phenylsulfonyl)butanamide;

N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-2-hydroxy-4-

difluorobenzyl)-3-[(3-ethynylbenzyl)amino]-2-hydroxypropyl)amino)carbonyl]propyl)-3-methyl-1H-pyrazole-5-carboxamide;

N-((1R)-3-(butylsulfonyl)-1-[[[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[3-(trifluoromethyl)benzyl]amino]propyl)amino]carbonyl]propyl)-3-methyl-1H-pyrazole-5-carboxamide;

N-((1R)-3-(butylsulfonyl)-1-[[[(1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethylphenyl)cyclopropyl]amino]-2-hydroxypropyl)amino]carbonyl]propyl)-3-methyl-1H-pyrazole-5-carboxamide;

N-((1R)-3-(butylsulfonyl)-1-[[[(1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethynylphenyl)cyclopropyl]amino]-2-hydroxypropyl)amino]carbonyl]propyl)-3-methyl-1H-pyrazole-5-carboxamide;

N-[(1R)-3-(butylsulfonyl)-1-[[[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-([1-[3-(trifluoromethyl)phenyl]cyclopropyl)amino]propyl]amino]carbonyl]propyl)-3-methyl-1H-pyrazole-5-carboxamide;

(2R)-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-[[[(methylamino)carbonyl]amino]-4-oxooctanamide;

4-butyl-N¹-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N²-[(methylamino)carbonyl]-D-homoserinamide;

3-(2-butyl-1,3-dioxolan-2-yl)-N¹-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N²-[(methylamino)carbonyl]-D-alaninamide;

3-(2-butyl-1,3-dioxan-2-yl)-N¹-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N²-[(methylamino)carbonyl]-D-alaninamide

(2R)-N-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4,4-difluoro-2-[[[(methylamino)carbonyl]amino]octanamide;

(2R)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-fluoro-2-
[(methyamino)carbonyl]amino}octanamide;

(2R)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-
[(methyamino)carbonyl]amino}-5-oxononanamide;

(2R)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-hydroxy-2-
[(methyamino)carbonyl]amino}nonanamide;

(2R)-4-(2-butyl-1,3-dioxolan-2-yl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-
[(methyamino)carbonyl]amino}butanamide;

(2R)-4-(2-butyl-1,3-dioxan-2-yl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-
[(methyamino)carbonyl]amino}butanamide;

(2R)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5-fluoro-2-
[(methyamino)carbonyl]amino}nonanamide;

(2R)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-5,5-difluoro-2-
[(methyamino)carbonyl]amino}nonanamide;

3-(butylsulfonyl)-N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethynylbenzyl)amino]-2-hydroxypropyl)-N²-
[(methyamino)carbonyl]-D-alaninamide;

3-(butylsulfonyl)-N¹-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-(trifluoromethyl)benzyl)amino]propyl)-N²-
[(methyamino)carbonyl]-D-alaninamide;

3-(butylsulfonyl)-N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(1-(3-ethylphenyl)cyclopropyl)amino]-2-hydroxypropyl)-N²-
[(methyamino)carbonyl]-D-alaninamide;

3-(butylsulfonyl)-N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(1-(3-ethynylphenyl)cyclopropyl)amino]-2-hydroxypropyl)-N²-
[(methyamino)carbonyl]-D-alaninamide;

3-(butylsulfonyl)-N¹-[(1S,2R)-1-(3,5-difluorobenzyl)-2-

hydroxy-3-((1-[3-

(trifluoromethyl)phenyl]cyclopropyl)amino)propyl]-N²-
[(methylamino)carbonyl]-D-alaninamide;

4-Methyl-pyrazole-1-carboxylic acid {2-(butane-1-sulfonyl)-1-[1-(3,5-difluoro-benzyl)-3-(3-ethynyl-benzylamino)-2-hydroxy-propylcarbamoyl]-ethyl}-amide;

4-Methyl-pyrazole-1-carboxylic acid {2-(butane-1-sulfonyl)-1-[1-(3,5-difluoro-benzyl)-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propylcarbamoyl]-ethyl}-amide;

4-Methyl-pyrazole-1-carboxylic acid {2-(butane-1-sulfonyl)-1-{1-(3,5-difluoro-benzyl)-3-[1-(3-ethyl-phenyl)-cyclopropylamino]-2-hydroxy-propylcarbamoyl}-ethyl}-amide;

4-Methyl-pyrazole-1-carboxylic acid {2-(butane-1-sulfonyl)-1-{1-(3,5-difluoro-benzyl)-3-[1-(3-ethynyl-phenyl)-cyclopropylamino]-2-hydroxy-propylcarbamoyl}-ethyl}-amide;

4-Methyl-pyrazole-1-carboxylic acid {2-(butane-1-sulfonyl)-1-{1-(3,5-difluoro-benzyl)-2-hydroxy-3-[1-(3-trifluoromethyl-phenyl)-cyclopropylamino]-propylcarbamoyl}-ethyl}-amide; and pharmaceutically acceptable salts thereof.

Definitions

All temperatures are in degrees Celsius.

TLC refers to thin-layer chromatography.

5 psi refers to pounds/in².

HPLC refers to high pressure liquid chromatography.

THF refers to tetrahydrofuran.

DMF refers to dimethylformamide.

HOBt refers to 1-hydroxy bezotriazole hydrate.

10 NMM refers to N-methyl morpholine.

EDC refers to ethyl-1-(3-dimethylaminopropyl)carbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride.

NBS refers to N-bromosuccinimide.

TEA refers to triethylamine.

BOC refers to 1,1-dimethylethoxy carbonyl or t-butoxycarbonyl, $-\text{CO}_2\text{C}(\text{CH}_3)_3$.

CBZ refers to benzyloxycarbonyl, $-\text{CO}_2\text{-CH}_2\text{-phenyl}$.

TFA refers to trifluoroacetic acid, CF_3COOH .

5 CDI refers to 1,1'-carbonyldiimidazole.

Saline refers to an aqueous saturated sodium chloride solution.

Chromatography (column and flash chromatography) refers to purification/separation of compounds expressed as (support,
10 eluent). It is understood that the appropriate fractions are pooled and concentrated to give the desired compound(s).

CMR refers to C-13 magnetic resonance spectroscopy, chemical shifts are reported in ppm (δ) downfield from TMS.

15 NMR refers to nuclear (proton) magnetic resonance spectroscopy, chemical shifts are reported in ppm (δ) downfield from TMS.

$-\phi$ refers to phenyl (C_6H_5).

MS refers to mass spectrometry expressed as m/e, m/z or mass/charge unit. MH^+ refers to the positive ion of a parent
20 plus a hydrogen atom. EI refers to electron impact. CI refers to chemical ionization. FAB refers to fast atom bombardment.

HRMS refers to high resolution mass spectrometry.

Ether refers to diethyl ether.

25 When solvent pairs are used, the ratios of solvents used are volume/volume (v/v).

When the solubility of a solid in a solvent is used the ratio of the solid to the solvent is weight/volume (wt/v).

BOP refers to benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate.

30 TBDMSCl refers to t-butyldimethylsilyl chloride.

TBDMSOTf refers to t-butyldimethylsilyl trifluosulfonic acid ester.

Trisomy 21 refers to Down's Syndrome.

CYCLOPHOS refers to *R*-1-cyclohexyl-1,2-bis(diphenylphosphino)ethane.

BDPP refers to (2*S*,4*S*)-bis(diphenylphosphine) pentane.

DEGPPOS refers to 1-substituted (*S,S*)-3,4-bis-(diphenylphosphino)- pyrrolidine.

PNNP refers to *N,N'*-bis(diphenylphosphino)-*N,N'*-bis[(*R*)-1-phenyl]ethylenediamine.

LDA refers to lithium diisopropylamide.

LiHMDS refers to lithium hexamethyldisilazane.

KHMDS refers to potassium hexamethyldisilazane.

By the terms "alkyl" and " C_1 - C_6 alkyl" is meant straight or branched chain alkyl groups having 1-6 carbon atoms, such as, methyl, ethyl, propyl, isopropyl, *n*-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl. It is understood that in cases where an alkyl chain of a substituent (e.g. of an alkyl, alkoxy or alkenyl group) is shorter or longer than 6 carbons, it will be so indicated in the second "C" as, for example, " C_1 - C_{10} " indicates a maximum of 10 carbons.

By the terms "alkoxy" and " C_1 - C_6 alkoxy" is meant straight or branched chain alkyl groups having 1-6 carbon atoms, attached through at least one divalent oxygen atom, such as, for example, methoxy, ethoxy, propoxy, isopropoxy, *n*-butoxy, sec-butoxy, tert-butoxy, pentoxy, isopentoxy, neopentoxy, hexoxy, and 3-methylpentoxy.

By the term "halogen" is meant fluorine, bromine, chlorine, and/or iodine.

The terms "alkenyl" and " C_2 - C_6 alkenyl" refer to straight and branched hydrocarbon radicals having from 2 to 6 carbon atoms and from one to three double bonds and includes, for example, ethenyl, propenyl, 1-but-3-enyl, 1-pent-3-enyl, 1-hex-5-enyl and the like.

The terms "alkynyl" and "C₂-C₆ alkynyl" means straight and branched hydrocarbon radicals having from 2 to 6 carbon atoms and one or two triple bonds and includes ethynyl, propynyl, butynyl, pentyn-2-yl and the like.

5 As used herein, the term "cycloalkyl" refers to saturated carbocyclic radicals having three to twelve carbon atoms. The cycloalkyl can be monocyclic, or a polycyclic fused system. Examples of such radicals include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. The cycloalkyl groups
10 herein are unsubstituted or, as specified, substituted in one or more substitutable positions with various groups. For example, such cycloalkyl groups may be optionally substituted with C₁-C₆ alkyl, C₁-C₆ alkoxy, halogen, hydroxy, cyano, nitro, amino, mono(C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, C₂-C₆alkenyl,
15 C₂-C₆alkynyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, amino(C₁-C₆)alkyl, mono(C₁-C₆)alkylamino(C₁-C₆)alkyl or di(C₁-C₆)alkylamino(C₁-C₆)alkyl.

By "aryl" is meant an aromatic carbocyclic group having a single ring (e.g., phenyl), multiple rings (e.g., biphenyl), or
20 multiple condensed rings in which at least one is aromatic, (e.g., 1,2,3,4-tetrahydronaphthyl, naphthyl), which is optionally mono-, di-, or trisubstituted. Preferred aryl groups of the invention are phenyl, 1-naphthyl, 2-naphthyl, indanyl, indenyl, dihydronaphthyl, tetralinyl or 6,7,8,9-
25 tetrahydro-5H-benzo[a]cycloheptenyl. Even more preferred aryl groups are phenyl and naphthyl. The most preferred aryl group is phenyl.

The aryl groups herein are unsubstituted or, as specified, substituted in one or more substitutable positions with various
30 groups. For example, such aryl groups may be optionally substituted with, for example, C₁-C₆ alkyl, C₁-C₆ alkoxy, halogen, hydroxy, cyano, nitro, amino, mono(C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, amino(C₁-C₆)alkyl, mono(C₁-C₆)alkylamino(C₁-

C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl, -COOH, -C(=O)O(C₁-C₆ alkyl), -C(=O)NH₂, -C(=O)N(mono- or di-C₁-C₆ alkyl), -S(C₁-C₆ alkyl), -SO₂(C₁-C₆ alkyl), -O-C(=O)(C₁-C₆ alkyl), -NH-C(=O)-(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)-C(=O)-(C₁-C₆ alkyl), -NH-SO₂-(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)-SO₂-(C₁-C₆ alkyl), -NH-C(=O)NH₂, -NH-C(=O)N(mono- or di-C₁-C₆ alkyl), -NH(C₁-C₆ alkyl)-C(=O)-NH₂ or -NH(C₁-C₆ alkyl)-C(=O)-N-(mono- or di-C₁-C₆ alkyl).

By "heteroaryl" is meant one or more aromatic ring systems of 5-, 6-, or 7-membered rings which includes fused ring systems of 9-11 atoms containing at least one and up to four heteroatoms selected from nitrogen, oxygen, or sulfur. Preferred heteroaryl groups of the invention include pyridinyl, pyrimidinyl, quinolinyl, benzothienyl, indolyl, indolinyl, pyridazinyl, pyrazinyl, isoindolyl, isoquinolyl, quinazolinyl, quinoxalinyl, phthalazinyl, imidazolyl, isoxazolyl, pyrazolyl, oxazolyl, thiazolyl, indolizinyl, indazolyl, benzothiazolyl, benzimidazolyl, benzofuranyl, furanyl, thienyl, pyrrolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, oxazolopyridinyl, imidazopyridinyl, isothiazolyl, naphthyridinyl, cinnolinyl, carbazolyl, beta-carbolinyl, isochromanlyl, chromanlyl, tetrahydroisoquinolinyl, isoindolinyl, isobenzotetrahydrofuranlyl, isobenzotetrahydrothienyl, isobenzothienyl, benzoxazolyl, pyridopyridinyl, benzotetrahydrofuranlyl, benzotetrahydrothienyl, purinyl, benzodioxolyl, triazinyl, phenoxazinyl, phenothiazinyl, pteridinyl, benzothiazolyl, imidazopyridinyl, imidazothiazolyl, dihydrobenzisoxazinyl, benzisoxazinyl, benzoxazinyl, dihydrobenzisothiazinyl, benzopyranlyl, benzothiopyranlyl, coumarinyl, isocoumarinyl, chromonyl, chromanonyl, pyridinyl-N-oxide, tetrahydroquinolinyl, dihydroquinolinyl, dihydroquinolinonyl, dihydroisoquinolinonyl, dihydrocoumarinyl, dihydroisocoumarinyl, isoindolinonyl, benzodioxanlyl, benzoxazolinonyl, pyrrolyl N-oxide, pyrimidinyl N-oxide, pyridazinyl N-oxide, pyrazinyl N-oxide, quinolinyl N-oxide,

indolyl N-oxide, indolinyl N-oxide, isoquinolyl N-oxide,
quinazolinyl N-oxide, quinoxalinyl N-oxide, phthalazinyl N-
oxide, imidazolyl N-oxide, isoxazolyl N-oxide, oxazolyl N-
oxide, thiazolyl N-oxide, indolizinyll N-oxide, indazolyl N-
5 oxide, benzothiazolyl N-oxide, benzimidazolyl N-oxide, pyrrolyl
N-oxide, oxadiazolyl N-oxide, thiadiazolyl N-oxide, triazolyl
N-oxide, tetrazolyl N-oxide, benzothiopyranyl S-oxide,
benzothiopyranyl S,S-dioxide.

The heteroaryl groups herein are unsubstituted or, as
10 specified, substituted in one or more substitutable positions
with various groups. For example, such heteroaryl groups may
be optionally substituted with C₁-C₆ alkyl, C₁-C₆ alkoxy,
halogen, hydroxy, cyano, nitro, amino, mono(C₁-C₆)alkylamino,
di(C₁-C₆)alkylamino, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆ haloalkyl,
15 C₁-C₆ haloalkoxy, amino(C₁-C₆)alkyl, mono(C₁-C₆)alkylamino(C₁-
C₆)alkyl or di(C₁-C₆)alkylamino(C₁-C₆)alkyl, -COOH, -C(=O)O(C₁-C₆
alkyl), -C(=O)NH₂, -C(=O)N(mono- or di-C₁-C₆ alkyl), -S(C₁-C₆
alkyl), -SO₂(C₁-C₆ alkyl), -O-C(=O)(C₁-C₆ alkyl), -NH-C(=O)-(C₁-
C₆ alkyl), -N(C₁-C₆ alkyl)-C(=O)-(C₁-C₆ alkyl), -NH-SO₂-(C₁-C₆
20 alkyl), -N(C₁-C₆ alkyl)-SO₂-(C₁-C₆ alkyl), -NH-C(=O)NH₂, -NH-
C(=O)N(mono- or di-C₁-C₆ alkyl), -NH(C₁-C₆ alkyl)-C(=O)-NH₂ or
-NH(C₁-C₆ alkyl)-C(=O)-N-(mono- or di-C₁-C₆ alkyl).

By the terms "heterocycle", "heterocycloalkyl" and
"heterocyclyl" is meant one or more carbocyclic ring systems of
25 4-, 5-, 6-, or 7-membered rings which includes fused ring
systems of 9-11 atoms containing at least one and up to four
heteroatoms selected from nitrogen, oxygen, or sulfur.
Preferred heterocycles of the invention include morpholinyl,
thiomorpholinyl, thiomorpholinyl S-oxide, thiomorpholinyl S,S-
30 dioxide, piperazinyl, homopiperazinyl, pyrrolidinyl,
pyrrolinyl, tetrahydropyranyl, piperidinyl, tetrahydrofuranyl,
tetrahydrothienyl, homopiperidinyl, homomorpholinyl,
homothiomorpholinyl, homothiomorpholinyl S,S-dioxide,
oxazolidinonyl, dihydropyrazolyl, dihydropyrrolyl,

dihydropyrazinyl, dihydropyridinyl, dihydropyrimidinyl, dihydrofuryl, dihydropyranyl, tetrahydrothienyl S-oxide, tetrahydrothienyl S,S-dioxide and homothiomorpholinyl S-oxide.

5 The heterocycle groups herein are unsubstituted or, as specified, substituted in one or more substitutable positions with various groups. For example, such heterocycle groups may be optionally substituted with C₁-C₆ alkyl, C₁-C₆ alkoxy, halogen, hydroxy, cyano, nitro, amino, mono(C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆ haloalkyl, 10 C₁-C₆ haloalkoxy, amino(C₁-C₆)alkyl, mono(C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl or =O.

APP, amyloid precursor protein, is defined as any APP polypeptide, including APP variants, mutations, and isoforms, for example, as disclosed in U.S. Patent No. 5,766,846.

15 A-beta, amyloid beta peptide, is defined as any peptide resulting from beta-secretase mediated cleavage of APP, including peptides of 39, 40, 41, 42, and 43 amino acids, and extending from the beta-secretase cleavage site to amino acids 39, 40, 41, 42, or 43.

20 Beta-secretase (BACE1, Asp2, Memapsin 2) is an aspartyl protease that mediates cleavage of APP at the amino-terminal edge of A-beta. Human beta-secretase is described, for example, in WO00/17369.

25 Pharmaceutically acceptable refers to those properties and/or substances that are acceptable to the patient from a pharmacological/toxicological point of view and to the manufacturing pharmaceutical chemist from a physical/chemical point of view regarding composition, formulation, stability, patient acceptance and bioavailability.

30 A therapeutically effective amount is defined as an amount effective to reduce or lessen at least one symptom of the disease being treated or to reduce or delay onset of one or more clinical markers or symptoms of the disease.

Pharmaceutical Compositions

Compositions containing therapeutically effective amounts of the compounds are provided of the invention. The compounds are preferably formulated into suitable pharmaceutical preparations such as tablets, capsules or elixirs, for oral administration or in sterile solutions or suspensions for parenteral administration. Typically the compounds described above are formulated into pharmaceutical compositions using techniques and procedures known in the art.

10 A unit dose of about 0.1 to 1000 mg of a compound or mixture of compounds of the invention or a physiologically acceptable salt is compounded with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, flavor, etc., in a unit dosage form as called for by accepted pharmaceutical practice. The amount of active substance in those compositions or preparations is such that a suitable dosage in the range indicated is obtained. The compositions are preferably formulated in a unit dosage form, each dosage containing from about 0.1 to about 1000 mg the desired amount of the active ingredient. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient. Preferably, the compound of the invention is employed at no more than about 20 weight percent of the pharmaceutical composition, more preferably no more than about 15 weight percent, with the balance being pharmaceutically inert carrier(s).

30 To prepare compositions, one or more compounds of the invention are mixed with a suitable pharmaceutically acceptable carrier. Upon mixing or addition of the compound(s), the resulting mixture may be a solution, suspension, emulsion or the like. Liposomal suspensions may also be suitable as

pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the selected carrier or vehicle. The effective concentration is sufficient for ameliorating at least one symptom of the disease, disorder, or condition treated and may be empirically determined.

Pharmaceutical carriers or vehicles suitable for administration of the compounds provided herein include any such carriers known to those skilled in the art to be suitable for the particular mode of administration. In addition, the active materials can also be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action or have other action. The compounds may be formulated as the sole pharmaceutically active ingredient in the composition or may be combined with other active ingredients.

In instances in which the compounds exhibit insufficient solubility, methods for solubilizing compounds may be used. Such methods are known to those of skill in this art, and include, but are not limited to, using cosolvents, such as dimethylsulfoxide (DMSO), using surfactants, such as Tween®, or dissolution in aqueous sodium bicarbonate. Derivatives of the compounds, such as salts of the compounds or prodrugs of the compounds may also be used in formulating effective pharmaceutical compositions.

The concentration of the compounds in the composition is effective for delivery of an amount that, upon administration, ameliorates one or more symptoms of the disorder for which the compound is administered. Typically, the compositions are formulated for single dosage administration.

The compounds of the invention may be prepared with carriers that protect them against rapid elimination from the

If oral administration is desired, the compound may be provided in a composition that protects it from the acidic environment of the stomach. For example, the composition can be formulated in an enteric coating that maintains its integrity in the stomach and releases the active compound in the intestine. The composition may also be formulated in combination with an antacid or other such ingredient.

Oral compositions will generally include an inert diluent or an edible carrier and may be compressed into tablets or enclosed in gelatin capsules. For the purpose of oral therapeutic administration, the active compound or compounds can be incorporated with excipients and used in the form of tablets, capsules or troches. Pharmaceutically compatible binding agents and adjuvant materials can be included as part of the composition.

The tablets, pills, capsules, troches, and the like can contain any of the following ingredients or compounds of a similar nature: a binder, such as, but not limited to, gum tragacanth, acacia, corn starch, or gelatin; an excipient such as microcrystalline cellulose, starch, or lactose; a disintegrating agent such as, but not limited to, alginic acid or corn starch; a lubricant such as, but not limited to, magnesium stearate; a gildant, such as, but not limited to, colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; and a flavoring agent such as peppermint, methyl salicylate, or fruit flavoring.

When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials that modify the physical form of the dosage unit, for example, coatings of sugar or other enteric agents. The compounds can also be administered as a component of an elixir, suspension, syrup, wafer, chewing gum, or the like. A syrup may contain, in addition to the active

compounds, sucrose as a sweetening agent or certain preservatives, dyes and colorings, and flavors.

The active materials can also be mixed with other active materials that do not impair the desired action, or with
5 materials that supplement the desired action.

Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application can include any of the following components: a sterile diluent, such as water for injection, saline solution, fixed oil, a naturally occurring
10 vegetable oil such as sesame oil, coconut oil, peanut oil, cottonseed oil, and the like, or a synthetic fatty vehicle such as ethyl oleate or the like, polyethylene glycol, glycerine, propylene glycol, or other synthetic solvent; antimicrobial agents, such as benzyl alcohol or methyl parabens;
15 antioxidants, such as ascorbic acid or sodium bisulfite; chelating agents, such as ethylenediaminetetraacetic acid (EDTA); buffers, such as acetates, citrates, or phosphates; and agents for the adjustment of tonicity, such as sodium chloride or dextrose. Parenteral preparations can be enclosed in
20 ampoules, disposable syringes, or multiple dose vials made of glass, plastic, or other suitable material. Buffers, preservatives, antioxidants, and the like can be incorporated as required.

If administered intravenously, suitable carriers include
25 physiological saline or phosphate buffered saline (PBS), and solutions containing thickening and solubilizing agents, such as glucose, polyethylene glycol, polypropyleneglycol, and mixtures thereof. Liposomal suspensions, including tissue-targeted liposomes, may also be suitable as pharmaceutically
30 acceptable carriers. These may be prepared according to methods known to those skilled in the art. For example, liposome formulations may be prepared as described in U.S. Pat. No. 4,522,811.

The active compounds may be prepared with carriers that protect the compound against rapid elimination from the body, such as time release formulations or coatings. Such carriers include controlled release formulations, such as, but not limited to, implants and microencapsulated delivery systems, and biodegradable, biocompatible polymers, such as collagen, ethylene vinyl acetate, polyanhydrides, polyglycolic acid, polyorthoesters, polylactic acid, and others. Methods for preparation of such formulations are known to those skilled in the art.

Methods of the Invention

The compounds of the invention, and pharmaceutically acceptable salts thereof, are useful for treating humans or animals suffering from a condition characterized by a pathological form of beta-amyloid peptide, such as beta-amyloid plaques, and for helping to prevent or delay the onset of such a condition. For example, the compounds are useful for treating Alzheimer's disease, for helping prevent or delay the onset of Alzheimer's disease, for treating patients with MCI (mild cognitive impairment) and preventing or delaying the onset of Alzheimer's disease in those who would progress from MCI to AD, for treating Down's syndrome, for treating humans who have Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, for treating cerebral amyloid angiopathy and preventing its potential consequences, i.e. single and recurrent lobar hemorrhages, for treating other degenerative dementias, including dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, diffuse Lewy body type Alzheimer's disease. The compounds and compositions of the invention are particularly useful for treating Alzheimer's disease. When treating these diseases,

the compounds of the invention can either be used individually or in combination, as is best for the patient.

As used herein, the term "treating" means that the compounds of the invention can be used in humans with at least a tentative diagnosis of disease. The compounds of the invention will delay or slow the progression of the disease thereby giving the individual a longer and more useful life span.

The term "preventing" means that the compounds of the invention are useful when administered to a patient who has not been diagnosed as having or possibly having the disease at the time of administration, but who would normally be expected to develop the disease or be at increased risk for the disease. The compounds of the invention will slow the development of disease symptoms, delay the onset of the disease, or prevent the individual from developing the disease. Preventing thus includes administration of the compounds of the invention to those individuals thought to be predisposed to the disease due to age, familial history, genetic or chromosomal abnormalities, and/or due to the presence of one or more biological markers for the disease, such as a known genetic mutation of APP or APP cleavage products in brain tissues or fluids.

In treating or preventing the above diseases, the compounds of the invention are administered in a therapeutically effective amount. The therapeutically effective amount will vary depending on the particular compound used and the route of administration, as is known to those skilled in the art.

In treating a patient displaying any of the diagnosed above conditions a physician may administer a compound of the invention immediately and continue administration indefinitely, as needed. In treating patients who are not diagnosed as having Alzheimer's disease, but who are believed to be at substantial risk for Alzheimer's disease, the physician should

preferably start treatment when the patient first experiences early pre-Alzheimer's symptoms such as, memory or cognitive problems associated with aging. In addition, there are some patients who may be determined to be at risk for developing
5 Alzheimer's through the detection of a genetic marker such as APOE4 or other biological indicators that are predictive for Alzheimer's disease. In these situations, even though the patient does not have symptoms of the disease, administration of the compounds of the invention may be started before
10 symptoms appear, and treatment may be continued indefinitely to prevent or delay the outset of the disease.

Modes of Administration, Dosage Forms and Amounts

The compounds of the invention can be administered orally,
15 parenterally (IV, IM, depo-IM, SQ and depo-SQ), sublingually, intranasally (inhalation), intrathecally, topically and rectally. Dosage forms known to those skilled in the art are suitable for delivery of the novel substituted amines X of the invention.

20 Compositions are provided that contain therapeutically effective amounts of the compounds of the invention. The compounds are preferably formulated into suitable pharmaceutical preparations such as tablets, capsules, or elixirs for oral administration or in sterile solutions or
25 suspensions for parenteral administration. Typically the compounds described above are formulated into pharmaceutical compositions using techniques and procedures known in the art.

About 1 to 500 mg of a compound or mixture of compounds of the invention or a physiologically acceptable salt or ester is
30 compounded with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, flavor, etc., in a unit dosage form as called for by accepted pharmaceutical practice. The amount of active substance in those compositions or preparations is such that a suitable dosage in the range

and include, but are not limited to, using cosolvents such as dimethylsulfoxide (DMSO), using surfactants such as Tween®, and dissolution in aqueous sodium bicarbonate. Derivatives of the compounds, such as salts or prodrugs may also be used in
5 formulating effective pharmaceutical compositions.

The concentration of the compound is effective for delivery of an amount upon administration that lessens or ameliorates at least one symptom of the disorder for which the compound is administered. Typically, the compositions are
10 formulated for single dosage administration.

The compounds of the invention may be prepared with carriers that protect them against rapid elimination from the body, such as time-release formulations or coatings. Such carriers include controlled release formulations, such as, but
15 not limited to, microencapsulated delivery systems. The active compound is included in the pharmaceutically acceptable carrier in an amount sufficient to exert a therapeutically useful effect in the absence of undesirable side effects on the patient treated. The therapeutically effective concentration
20 may be determined empirically by testing the compounds in known *in vitro* and *in vivo* model systems for the treated disorder.

The compounds and compositions of the invention can be enclosed in multiple or single dose containers. The enclosed compounds and compositions can be provided in kits, for
25 example, including component parts that can be assembled for use. For example, a compound inhibitor in lyophilized form and a suitable diluent may be provided as separated components for combination prior to use. A kit may include a compound inhibitor and a second therapeutic agent for co-administration.
30 The inhibitor and second therapeutic agent may be provided as separate component parts. A kit may include a plurality of containers, each container holding one or more unit dose of the compound of the invention. The containers are preferably adapted for the desired mode of administration, including, but

not limited to tablets, gel capsules, sustained-release capsules, and the like for oral administration; depot products, pre-filled syringes, ampules, vials, and the like for parenteral administration; and patches, medipads, creams, and
5 the like for topical administration.

The concentration of active compound in the drug composition will depend on absorption, inactivation, and excretion rates of the active compound, the dosage schedule, and amount administered as well as other factors known to those of
10 skill in the art.

The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at intervals of time. It is understood that the precise dosage and duration of treatment is a function of the disease being
15 treated and may be determined empirically using known testing protocols or by extrapolation from in vivo or in vitro test data. It is to be noted that concentrations and dosage values may also vary with the severity of the condition to be alleviated. It is to be further understood that for any
20 particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only and are not intended
25 to limit the scope or practice of the claimed compositions.

If oral administration is desired, the compound should be provided in a composition that protects it from the acidic environment of the stomach. For example, the composition can be formulated in an enteric coating that maintains its integrity
30 in the stomach and releases the active compound in the intestine. The composition may also be formulated in combination with an antacid or other such ingredient.

Oral compositions will generally include an inert diluent or an edible carrier and may be compressed into tablets or

enclosed in gelatin capsules. For the purpose of oral therapeutic administration, the active compound or compounds can be incorporated with excipients and used in the form of tablets, capsules, or troches. Pharmaceutically compatible
5 binding agents and adjuvant materials can be included as part of the composition.

The tablets, pills, capsules, troches, and the like can contain any of the following ingredients or compounds of a similar nature: a binder such as, but not limited to, gum
10 tragacanth, acacia, corn starch, or gelatin; an excipient such as microcrystalline cellulose, starch, or lactose; a disintegrating agent such as, but not limited to, alginic acid and corn starch; a lubricant such as, but not limited to,
magnesium stearate; a gildant, such as, but not limited to,
15 colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; and a flavoring agent such as peppermint, methyl salicylate, or fruit flavoring.

When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such
20 as a fatty oil. In addition, dosage unit forms can contain various other materials, which modify the physical form of the dosage unit, for example, coatings of sugar and other enteric agents. The compounds can also be administered as a component of an elixir, suspension, syrup, wafer, chewing gum or the
25 like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings, and flavors.

The active materials can also be mixed with other active materials that do not impair the desired action, or with
30 materials that supplement the desired action.

Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application can include any of the following components: a sterile diluent such as water for injection, saline solution, fixed oil, a naturally occurring

vegetable oil such as sesame oil, coconut oil, peanut oil, cottonseed oil, and the like, or a synthetic fatty vehicle such as ethyl oleate, and the like, polyethylene glycol, glycerine, propylene glycol, or other synthetic solvent; antimicrobial

5 agents such as benzyl alcohol and methyl parabens; antioxidants such as ascorbic acid and sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid (EDTA); buffers such as acetates, citrates, and phosphates; and agents for the adjustment of tonicity such as sodium chloride and dextrose.

10 Parenteral preparations can be enclosed in ampoules, disposable syringes, or multiple dose vials made of glass, plastic, or other suitable material. Buffers, preservatives, antioxidants, and the like can be incorporated as required.

Where administered intravenously, suitable carriers

15 include physiological saline, phosphate buffered saline (PBS), and solutions containing thickening and solubilizing agents such as glucose, polyethylene glycol, polypropyleneglycol, and mixtures thereof. Liposomal suspensions including tissue-targeted liposomes may also be suitable as pharmaceutically

20 acceptable carriers. These may be prepared according to methods known for example, as described in U.S. Patent No. 4,522,811.

The active compounds may be prepared with carriers that protect the compound against rapid elimination from the body,

25 such as time-release formulations or coatings. Such carriers include controlled release formulations, such as, but not limited to, implants and microencapsulated delivery systems, and biodegradable, biocompatible polymers such as collagen, ethylene vinyl acetate, polyanhydrides, polyglycolic acid,

30 polyorthoesters, polylactic acid, and the like. Methods for preparation of such formulations are known to those skilled in the art.

The compounds of the invention can be administered orally, parenterally (IV, IM, depo-IM, SQ, and depo-SQ), sublingually,

intranasally (inhalation), intrathecally, topically, or rectally. Dosage forms known to those skilled in the art are suitable for delivery of the compounds of the invention.

Compounds of the invention may be administered enterally
5 or parenterally. When administered orally, compounds of the invention can be administered in usual dosage forms for oral administration as is known to those skilled in the art. These dosage forms include the usual solid unit dosage forms of tablets and capsules as well as liquid dosage forms such as
10 solutions, suspensions, and elixirs. When the solid dosage forms are used, it is preferred that they be of the sustained release type so that the compounds of the invention need to be administered only once or twice daily.

The oral dosage forms are administered to the patient 1,
15 2, 3, or 4 times daily. It is preferred that the compounds of the invention be administered either three or fewer times, more preferably once or twice daily. Hence, it is preferred that the compounds of the invention be administered in oral dosage form. It is preferred that whatever oral dosage form is used,
20 that it be designed so as to protect the compounds of the invention from the acidic environment of the stomach. Enteric coated tablets are known to those skilled in the art. In addition, capsules filled with small spheres each coated to protect from the acidic stomach, are also known to those
25 skilled in the art.

When administered orally, an administered amount therapeutically effective to inhibit beta-secretase activity, to inhibit A-beta production, to inhibit A-beta deposition, or to treat or prevent AD is from about 0.1 mg/day to about 1,000
30 mg/day. It is preferred that the oral dosage is from about 1 mg/day to about 100 mg/day. It is more preferred that the oral dosage is from about 5 mg/day to about 50 mg/day. It is understood that while a patient may be started at one dose,

that dose may be varied over time as the patient's condition changes.

Compounds of the invention may also be advantageously delivered in a nano crystal dispersion formulation.

5 Preparation of such formulations is described, for example, in U.S. Patent 5,145,684. Nano crystalline dispersions of HIV protease inhibitors and their method of use are described in US 6,045,829. The nano crystalline formulations typically afford greater bioavailability of drug compounds.

10 The compounds of the invention can be administered parenterally, for example, by IV, IM, depo-IM, SC, or depo-SC. When administered parenterally, a therapeutically effective amount of about 0.5 to about 100 mg/day, preferably from about 5 to about 50 mg daily should be delivered. When a depo
15 formulation is used for injection once a month or once every two weeks, the dose should be about 0.5 mg/day to about 50 mg/day, or a monthly dose of from about 15 mg to about 1,500 mg. In part because of the forgetfulness of the patients with Alzheimer's disease, it is preferred that the parenteral dosage
20 form be a depo formulation.

The compounds of the invention can be administered sublingually. When given sublingually, the compounds of the invention should be given one to four times daily in the amounts described above for IM administration.

25 The compounds of the invention can be administered intranasally. When given by this route, the appropriate dosage forms are a nasal spray or dry powder, as is known to those skilled in the art. The dosage of the compounds of the invention for intranasal administration is the amount described
30 above for IM administration.

The compounds of the invention can be administered intrathecally. When given by this route the appropriate dosage form can be a parenteral dosage form as is known to those skilled in the art. The dosage of the compounds of the

invention for intrathecal administration is the amount described above for IM administration.

The compounds of the invention can be administered topically. When given by this route, the appropriate dosage form is a cream, ointment, or patch. Because of the amount of the compounds of the invention to be administered, the patch is preferred. When administered topically, the dosage is from about 0.5 mg/day to about 200 mg/day. Because the amount that can be delivered by a patch is limited, two or more patches may be used. The number and size of the patch is not important, what is important is that a therapeutically effective amount of the compounds of the invention be delivered as is known to those skilled in the art. The compounds of the invention can be administered rectally by suppository as is known to those skilled in the art. When administered by suppository, the therapeutically effective amount is from about 0.5 mg to about 500 mg.

The compounds of the invention can be administered by implants as is known to those skilled in the art. When administering a compound of the invention by implant, the therapeutically effective amount is the amount described above for depot administration.

The invention here is the new compounds of the invention and new methods of using the compounds of the invention. Given a particular compound of the invention and a desired dosage form, one skilled in the art would know how to prepare and administer the appropriate dosage form.

The compounds of the invention are used in the same manner, by the same routes of administration, using the same pharmaceutical dosage forms, and at the same dosing schedule as described above, for treating patients with MCI (mild cognitive impairment) and preventing or delaying the onset of Alzheimer's disease in those who would progress from MCI to AD, for treating Down's syndrome, for treating humans who have

Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, for treating cerebral amyloid angiopathy and preventing its potential consequences, i.e. single and recurrent lobar hemorrhages, for treating other degenerative dementias, including dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, diffuse Lewy body type of Alzheimer's disease.

10 The compounds of the invention can be used in combination, with each other or with other therapeutic agents or approaches used to treat or prevent the conditions listed above. Such agents or approaches include: acetylcholine esterase inhibitors such as tacrine (tetrahydroaminoacridine, marketed
15 as COGNEX®), donepezil hydrochloride, (marketed as Aricept® and rivastigmine (marketed as Exelon®); gamma-secretase inhibitors; anti-inflammatory agents such as cyclooxygenase II inhibitors; anti-oxidants such as Vitamin E and ginkgolides; immunological approaches, such as, for example, immunization
20 with A-beta peptide or administration of anti-A-beta peptide antibodies; statins; and direct or indirect neurotropic agents such as Cerebrolysin®, AIT-082 (Emilieu, 2000, Arch. Neurol. 57:454), and other neurotropic agents of the future.

In addition, the compounds of the invention can also be
25 used with inhibitors of P-glycoprotein (P-gp). The use of P-gp inhibitors is known to those skilled in the art. See for example, *Cancer Research*, 53, 4595-4602 (1993), *Clin. Cancer Res.*, 2, 7-12 (1996), *Cancer Research*, 56, 4171-4179 (1996), International Publications WO99/64001 and WO01/10387. The
30 important thing is that the blood level of the P-gp inhibitor be such that it exerts its effect in inhibiting P-gp from decreasing brain blood levels of the compounds of the invention. To that end the P-gp inhibitor and the compounds of the invention can be administered at the same time, by the same

or different route of administration, or at different times. The important thing is not the time of administration but having an effective blood level of the P-gp inhibitor.

Suitable P-gp inhibitors include cyclosporin A, verapamil, tamoxifen, quinidine, Vitamin E-TGPS, ritonavir, megestrol acetate, progesterone, rapamycin, 10,11-methanodibenzosuberane, phenothiazines, acridine derivatives such as GF120918, FK506, VX-710, LY335979, PSC-833, GF-102,918 and other steroids. It is to be understood that additional agents will be found that do the same function and are also considered to be useful.

The P-gp inhibitors can be administered orally, parenterally, (IV, IM, IM-depo, SQ, SQ-depo), topically, sublingually, rectally, intranasally, intrathecally and by implant.

The therapeutically effective amount of the P-gp inhibitors is from about 0.1 to about 300 mg/kg/day, preferably about 0.1 to about 150 mg/kg daily. It is understood that while a patient may be started on one dose, that dose may have to be varied over time as the patient's condition changes.

When administered orally, the P-gp inhibitors can be administered in usual dosage forms for oral administration as is known to those skilled in the art. These dosage forms include the usual solid unit dosage forms of tablets and capsules as well as liquid dosage forms such as solutions, suspensions and elixirs. When the solid dosage forms are used, it is preferred that they be of the sustained release type so that the P-gp inhibitors need to be administered only once or twice daily. The oral dosage forms are administered to the patient one thru four times daily. It is preferred that the P-gp inhibitors be administered either three or fewer times a day, more preferably once or twice daily. Hence, it is preferred that the P-gp inhibitors be administered in solid dosage form and further it is preferred that the solid dosage form be a sustained release form which permits once or twice

daily dosing. It is preferred that what ever dosage form is used, that it be designed so as to protect the P-gp inhibitors from the acidic environment of the stomach. Enteric coated tablets are known to those skilled in the art. In addition, capsules filled with small spheres each coated to protect from the acidic stomach, are also known to those skilled in the art.

In addition, the P-gp inhibitors can be administered parenterally. When administered parenterally they can be administered IV, IM, depo-IM, SQ or depo-SQ.

The P-gp inhibitors can be given sublingually. When given sublingually, the P-gp inhibitors should be given one thru four times daily in the same amount as for IM administration.

The P-gp inhibitors can be given intranasally. When given by this route of administration, the appropriate dosage forms are a nasal spray or dry powder as is known to those skilled in the art. The dosage of the P-gp inhibitors for intranasal administration is the same as for IM administration.

The P-gp inhibitors can be given intrathecally. When given by this route of administration the appropriate dosage form can be a parenteral dosage form as is known to those skilled in the art.

The P-gp inhibitors can be given topically. When given by this route of administration, the appropriate dosage form is a cream, ointment or patch. Because of the amount of the P-gp inhibitors needed to be administered the patch is preferred. However, the amount that can be delivered by a patch is limited. Therefore, two or more patches may be required. The number and size of the patch is not important, what is important is that a therapeutically effective amount of the P-gp inhibitors be delivered as is known to those skilled in the art.

The P-gp inhibitors can be administered rectally by suppository as is known to those skilled in the art.

The P-gp inhibitors can be administered by implants as is known to those skilled in the art.

There is nothing novel about the route of administration nor the dosage forms for administering the P-gp inhibitors.

5 Given a particular P-gp inhibitor, and a desired dosage form, one skilled in the art would know how to prepare the appropriate dosage form for the P-gp inhibitor.

10 It should be apparent to one skilled in the art that the exact dosage and frequency of administration will depend on the particular compound administered, the particular condition being treated, the severity of the condition being treated, the age, weight, general physical condition of the particular patient, other medication the individual may be taking as is known to those skilled in the art.

15 The invention provides compounds, compositions, and methods for inhibiting beta-secretase enzyme activity and A-beta peptide production. Inhibition of beta-secretase enzyme activity halts or reduces the production of A-beta from APP and reduces or eliminates the formation of beta-amyloid deposits in
20 the brain.

The invention provides compounds, compositions, kits, and methods for inhibiting beta-secretase enzyme activity and A-beta peptide production. Inhibition of beta-secretase enzyme activity halts or reduces the production of A-beta from APP and
25 reduces or eliminates the formation of beta-amyloid deposits in the brain.

The invention provides compounds that are useful in treating and preventing Alzheimer's disease. The compounds of the invention are made by methods known to those skilled in the
30 art from starting materials either known to those skilled in the art, commercially available and/or that can be prepared readily using literature methods. The process chemistry is known to those skilled in the art. A general process to prepare the compounds of formula X is set forth in SCHEME A.

The chemistry is straight forward and in summary involves the steps of N-protecting the amino acid (I) starting material to produce the corresponding protected amino acid (II), reaction of the protected amino acid (II) with diazomethane followed by
5 work-up as described below to add a carbon atom to produce the corresponding protected compound (III), reduction of the protected halide to the corresponding alcohol (IV), formation of the corresponding epoxide (V), opening of the epoxide (V) with a C-terminal amine, R_C-NH_2 (VI) to produce the
10 corresponding protected alcohol (VII) which then has the nitrogen protecting group removed to produce the corresponding amine (VIII), which is then reacted with an amide forming agent such as, for example, $(R_N)_2O$ or R_N-X or R_N-OH (IX) to produce the compounds of formula X. One skilled in the art will
15 appreciate that these are all known reactions in organic chemistry. A chemist skilled in the art, knowing the chemical structure of the biologically active substituted amine end product X of the invention would be able to prepare them by known methods from known starting materials without any
20 additional information. The explanation below therefore is not necessary but is deemed helpful to those skilled in the art who desire to make the compounds of the invention.

The backbone of the compounds of the invention can be considered a hydroxyethylamine moiety, $-NH-CH(R)-CH(OH)-$. It
25 can be prepared by methods disclosed in the literature and known to those skilled in the art. For example, *J. Med. Chem.*, 36, 288-291 (1993), *Tetrahedron Letters*, 28, 5569-5572 (1987), *J. Med. Chem.*, 38, 581-584 (1995) and *Tetrahedron Letters*, 38, 619-620 (1997) and WO 02/02506 all disclose processes to
30 prepare hydroxyethylamine type compounds and/or their intermediates.

SCHEME A sets forth a general method used in the invention to prepare the appropriately substituted amines X. The compounds of the invention are prepared by starting with the

corresponding amino acid (I). The amino acids (I) are known to those skilled in the art or can be readily prepared by methods known to those skilled in the art. The compounds of the invention have at least two chiral centers, which give 2 sets
5 of diastereomers, each of which is racemic for a total of at least four stereoisomers. While biologically active end products result from all stereoisomers, the (S,R) configuration is preferred. The first of these chiral centers (the carbon carrying R₁) derives from the amino acid starting material (I).
10 It is preferred to commercially obtain or produce the desired enantiomer rather than produce an enantiomerically impure mixture and then have to separate out the desired enantiomer. Thus it is preferred to start the process with enantiomerically pure (S)-amino acid (I) of the same configuration as that of
15 the desired X product.

In Scheme A, the protection of free amine (I) to produce the (S)-protected amino acid (II) is depicted. Amino protecting groups are known to those skilled in the art. See for
20 example, "Protecting Groups in Organic Synthesis", John Wiley and sons, New York, N.Y., 1981, Chapter 7; "Protecting Groups in Organic Chemistry", Plenum Press, New York, N.Y., 1973, Chapter 2. The function of the amino protecting group is to protect the free amino functionality (-NH₂) during subsequent
25 reactions on the (S)-amino acid (I) which would not proceed either because the amino group would react and be functionalized in a way that is inconsistent with its need to be free for subsequent reactions or the free amino group would interfere in the reaction. When the amino protecting group is
30 no longer needed, it is removed by methods known to those skilled in the art. By definition the amino protecting group must be readily removable as is known to those skilled in the art by methods known to those skilled in the art. Suitable amino PROTECTING GROUPS include *t*-butoxycarbonyl,

benzyloxycarbonyl, formyl, trityl, phthalimido,
trichloroacetyl, chloroacetyl, bromoacetyl, iodoacetyl, 4-
phenylbenzyloxycarbonyl, 2-methylbenzyloxycarbonyl, 4-
ethoxybenzyloxycarbonyl, 4-fluorobenzyloxycarbonyl, 4-
5 chlorobenzyloxycarbonyl, 3-chlorobenzyloxycarbonyl, 2-
chlorobenzyloxycarbonyl, 2,4-dichlorobenzyloxycarbonyl, 4-
bromobenzyloxycarbonyl, 3-bromobenzyloxycarbonyl, 4-
nitrobenzyloxycarbonyl, 4-cyanobenzyloxycarbonyl, 2-(4-
xenyl)isopropoxycarbonyl, 1,1-diphenyleth-1-yloxycarbonyl, 1,1-
10 diphenylprop-1-yloxycarbonyl, 2-phenylprop-2-yloxycarbonyl, 2-
(p-toluy1)prop-2-yloxycarbonyl, cyclopentanyloxycarbonyl, 1-
methylcycoopentanyloxycarbonyl, cyclohexanyloxycarbonyl, 1-
methylcyclohexanyloxycabonyl, 2-methylcyclohexanyloxycarbonyl, .
2-(4-toluy1sulfonyl)ethoxycarbonyl, 2-
15 (methy1sulfonyl)ethoxycarbonyl, 2-
(triphenylphosphino)ethoxycarbonyl, fluorenylmethoxycarbonyl,
2-(trimethylsilyl)ethoxycarbonyl, allyloxycarbonyl, 1-
(trimethylsilylmethyl)prop-1-enyloxycarbonyl, 5-
benzisoxalylmethoxycarbonyl, 4-acetoxybenzyloxycarbonyl, 2,2,2-
20 trichloroethoxycarbonyl, 2-ethynyl-2-propoxycarbonyl,
cyclopropylmethoxycarbonyl, 4-(decyloxyl)benzyloxycarbonyl,
isobrornyloxycarbonyl, 1-piperidyloxycarbonyl, 9-
fluoroenylmethyl carbonate, -CH=CH₂ and phenyl-C(=N)-H.

It is preferred that the protecting group be t-
25 butoxycarbonyl (BOC) and/or benzyloxycarbonyl (CBZ), it is more
preferred that the protecting group be t-butoxycarbonyl. One
skilled in the art will understand the preferred methods of
introducing a t-butoxycarbonyl or benzyloxycarbonyl protecting
group and may additionally consult T.W. Green and P.G.M. Wuts
30 in "Protective Groups in Organic Chemistry, John Wiley and
Sons, 1991 for guidance.

The (S)-protected amino acid (II) is transformed to the
corresponding (S)-protected compound (III) by two different
methods depending on nature of R₂ and R₃.

R_2 and R_3 can be the same or different. It is preferred that R_2 and R_3 both be $-H$. If R_2 and R_3 are not the same, an additional chiral or stereogenic center is added to the molecule. To produce compounds of formula (III) where R_2 and R_3 are both $-H$, the (S)-protected amino acid (II) is reacted with diazomethane, as is known to those skilled in the art, followed by reaction with a compound of the formula $H-X_1$ to produce the (S)-protected compound (III). X_1 includes $-Cl$, $-Br$, $-I$, $-O$ -tosylate, $-O$ -mesylate, $-O$ -nosylate and $-O$ -brosylate. It is preferred that $-X_1$ be $-Br$ or $-Cl$. Suitable reaction conditions include running the reaction in inert solvents, such as but not limited to ether, tetrahydrofuran and the like. The reactions from the (S)-protected amino acid (II) to the (S)-protected compound (III) are carried out for a period of time between 10 minutes and 1 day and at temperatures ranging from about -78° to about $20-25^\circ$. It is preferred to conduct the reactions for a period of time between 1-4 hours and at temperatures between -30° to -10° . This process adds one methylene group.

Alternatively, the (S)-protected compounds of formula (III) can be prepared by first converting the (S)-protected amino acid (II) to a corresponding methyl or ethyl ester, according to methods established in the art, followed by treatment with a reagent of formula $X_1-C(R_2)(R_3)-X_1$ and a strong metal base. The base serves to affect a halogen-metal exchange, where the $-X_1$ undergoing exchange is a halogen selected from chlorine, bromine or iodine. The nucleophilic addition to the ester derivative gives directly the (S)-protected compound (III). Suitable bases include, but are not limited to the alkylolithiums including, for example, *sec*-butyllithium, *n*-butyllithium, and *t*-butyllithium. The reactions are preferably conducted at low temperature, such as -78° . Suitable reaction conditions include running the reaction in inert solvents, such as but not limited to, ether,

tetrahydrofuran and the like. Where R_2 and R_3 are both hydrogen, then examples of $X_1-C(R_2)(R_3)-X_1$ include dibromomethane, diiodomethane, chloriodomethane, bromiodomethane and bromochloromethane. One skilled in the art knows the preferred conditions required to conduct this reaction. Furthermore, if R_2 and/or R_3 are not $-H$, then by the addition of $-C(R_2)(R_3)-X_1$ to esters of the (S)-protected amino acid (II) to produce the (S)-protected compound (III), an additional chiral center will be incorporated into the product, provided that R_2 and R_3 are not the same.

The (S)-protected compound (III) is then reduced by means known to those skilled in the art for reduction of a ketone to the corresponding secondary alcohol affording the corresponding alcohol (IV). The means and reaction conditions for reducing the (S)-protected compound (III) to the corresponding alcohol (IV) include, for example, sodium borohydride, lithium borohydride, borane, diisobutylaluminum hydride, and lithium aluminium hydride. Sodium borohydride is the preferred reducing agent. The reductions are carried out for a period of time between 1 hour and 3 days at temperatures ranging from -78° to elevated temperature up to the reflux point of the solvent employed. It is preferred to conduct the reduction between -78° and 0° . If borane is used, it may be employed as a complex, for example, borane-methyl sulfide complex, borane-piperidine complex, or borane-tetrahydrofuran complex. The preferred combination of reducing agents and reaction conditions needed are known to those skilled in the art, see for example, Larock, R.C. in Comprehensive Organic Transformations, VCH Publishers, 1989. The reduction of the (S)-protected compound (III) to the corresponding alcohol (IV) produces the second chiral center (third chiral center if R_2 and R_3 are not the same). The reduction of the (S)-protected compound (III) produces a mixture of enantiomers at the second center, (S, R/S)-alcohol (IV). This enantiomeric mixture is

then separated by means known to those skilled in the art such as selective low-temperature recrystallization or chromatographic separation, for example by HPLC, employing commercially available chiral columns. The enantiomer that is
5 used in the remainder of the process of SCHEME A is the (S,S)-alcohol (IV) since this enantiomer will give the desired biologically active anti-Alzheimer (S,R)-substituted amine X.

The (S, S)-alcohol (IV) is transformed to the corresponding epoxide (V) by means known to those skilled in
10 the art. The stereochemistry of the (S)-(IV) center is maintained in forming the epoxide (V). A preferred means is by reaction with base, for example, but not limited to, hydroxide ion generated from sodium hydroxide, potassium hydroxide, lithium hydroxide and the like. Reaction conditions include
15 the use of C₁-C₆ alcohol solvents; ethanol is preferred. A common co-solvent, such as for example, ethyl acetate may also be employed. Reactions are conducted at temperatures ranging from -45° up to the reflux temperature of the alcohol employed; preferred temperature ranges are between -20° and 40°.

20 An alternative, and preferable process for preparing the epoxide (V) when R₁ is 3,5-difluorobenzyl, is set forth in SCHEME E. The first step of the process is to protect the free amino group of the (S)-amino acid (I) with an amino protecting group, PROTECTING GROUP, as previously discussed to produce the
25 (S)-protected amino acid (II).

In the alternative process, the (S)-protected amino acid (I) is transformed to the corresponding (S)-protected ester (XVII) in one of a number of ways. One method involves the use of lithium hydroxide. Using lithium hydroxide, the (S)-
30 protected amino acid (I) and the lithium hydroxide are mixed and cooled to from about -20° to about 10°. Next a methylating agent, selected from the group consisting of dimethylsulfate, methyl iodide and methyl triflate, is added. It is more

preferred that the methylating agent is dimethylsulfate. This is followed by heating to from about 20° to about 50°.

Alternatively, the (S)-protected amino acid (I) is contacted with a weak base such as bicarbonate or preferably carbonate. This is followed by addition of the methylating agent. Heat is not necessary but can be used to facilitate the reaction. The carbonate method is known to those skilled in the art. For those (S)-protected esters (XVII) where Z₁ is not methyl, one skilled in the art knowing the chemical structure would know how to prepare the desired compounds from known starting materials. In one known method the (S)-protected amino acid (I) is contacted with an activating agent, such as DCC, followed addition of the appropriate alcohol, Z₁-OH. This method is operable when Z₁ is C₁-C₄ alkyl (optionally substituted), -CH₂-CH=CH₂ or phenyl (optionally substituted).

SCHEME F and PREPARATIONS 10 and 11 set forth an alternative process for the preparation of the ester (II). In the process of SCHEME F, the aldehyde (XX), which is known to those skilled in the art, is reacted with the phosphorous compound (XXI), where X₃ is a good leaving group, to produce the olefin (XXI). The phosphorous compounds (XXI) are known to those skilled in the art. It is preferred that X₃ is C₁-C₃ alkyl; it is more preferred that X₃ is C₁ alkyl. The aldehyde (XX) and the phosphate (XXI) are combined in an organic solvent then cooled to about 0°. A base such as DBU or TMG is added and the contents of the reaction mixture are warmed to about 20-25° and stirred until the reaction is complete. Once the reaction is complete, it is preferred to separate the E- and Z-olefin isomers (XXII). The separation is done by methods known to those skilled in the art, such as by silica gel chromatography. Next the olefin (XXII) is hydrogenated with a suitable hydrogenation catalyst to obtain the desired ester (II). Some hydrogenation reactions will give racemic ester (II). The desired stereochemistry of the ester (II) is (S)-,

and therefore it is preferable to use the Z-olefin (XXII) with a hydrogenation catalyst. It is preferred that the hydrogenation catalyst is a compound of the formula $[Rh(\text{diene})L]^+X^-$

5 where Rh is rhodium;

 where diene is cyclooctadiene and nonbornadiene;

 where L is DIPMAP, MeDuPhos, EtDuPhos, Binaphane, f-Binaphane, Me-KetalPhos, Me-f-KetalPhos, BINAP, DIOP, BPPFA, BPPM, CHIRAPHOS, PROPHOS, NORPHOS, CYCLOPHOS, BDPP, DEGPHOS,
10 PNMP and where X^- is ClO_4^- , BF_4^- , $CF_3-SO_3^-$, Cl^- , Br^- , PF_6^- and SbF_6^- . It is preferred that the hydrogenation catalyst be either DIPMAP or EtDuPhos. Suitable solvents include polar solvents such as alcohols, preferably C_1-C_5 alcohols and THF, more preferably methanol, ethanol, isopropanol and THF. The
15 chiral hydrogenation is performed in a temperature range of from about -20° to about reflux. It is preferred that the reaction be performed in the temperature range from about 0° to about room temperature (25°). The chiral hydrogenation is performed under a pressure of from about one atmosphere to
20 about 100 psig; it is more preferred that the chiral hydrogenation be performed under a pressure of from about 10 psig to about 40 psig.

 The (S)-protected ester (II) is then transformed to the corresponding (S)-protected ketone (III) by reaction with a
25 slight excess of a compound of the formula CH_2ClX^2 where X^2 is -Br and -I in one of two different ways. In one process, no exogenous nucleophile is used. That process requires (1) the presence of three or more equivalents of strong base which has a pK_b of greater than about 30 followed by (2) adding acid.
30 The other process requires (1) the presence of about 2 to about 2.5 equivalents of strong base which has a pK_b of greater than about 30, (2) contacting the mixture of step (1) with about 1 to about 1.5 equivalents of an exogenous nucleophile and (3) adding acid. Suitable strong bases are those which has a pK_b

of greater than about 30. It is preferred that the strong base be selected from the group consisting of LDA, LiHMDS and KHMDS; it is more preferred that the strong base be LDA. Suitable acids are those, which have a pK_a of less than about 10. It is preferred the acid be selected from the group consisting of acetic, sulfuric, hydrochloric, citric, phosphoric and benzoic acids; it is more preferred that the acid be acetic acid. The preferred solvent for the process is THF. The reaction can be performed in the temperature range from about -80° to about -50° ; it is preferred to perform the reaction in the temperature range of from about -75° to about -65° . Suitable nucleophiles include alkyl lithium, aryl lithium, alkyl-Grignard and aryl-Grignard reagents. It is preferred that the nucleophile be selected from the group consisting of phenyl lithium, n-butyl lithium, methyl magnesium bromide, methyl magnesium chloride, phenyl magnesium bromide, phenyl magnesium chloride; it is more preferred that the nucleophile be n-butyl lithium. PREPARATION 2 discloses the process with no nucleophile and PREPARATION 16 discloses the process with an exogenous nucleophile.

The (S)-protected ketone (III) is then reduced to the corresponding (S)-alcohol (IV) by means known to those skilled in the art for reduction of a ketone to the corresponding secondary alcohol. The means and reaction conditions for reducing the (S)-protected compound (III) to the corresponding alcohol (IV) include, for example, sodium borohydride, lithium borohydride, borane, diisobutylaluminum hydride, zinc borohydride and lithium aluminium hydride. Sodium borohydride is the preferred reducing agent. The reductions are carried out for a period of time between about 1 hour and about 3 days at temperatures ranging from about -78° to elevated temperature up to the reflux point of the solvent employed. It is preferred to conduct the reduction between about -78° and about 0° . If borane is used, it may be employed as a complex, for

example, borane-methyl sulfide complex, borane-piperidine complex, or borane-tetrahydrofuran complex. The preferred combination of reducing agents and reaction conditions needed are known to those skilled in the art, see for example, Larock,
5 R.C. in Comprehensive Organic Transformations, VCH Publishers, 1989. The reduction of the (S)-protected compound (III) to the corresponding alcohol (IV) produces a second chiral center. The reduction of the (S)-protected compound (III) produces a mixture of diastereomers at the second center, (S, R/S)-alcohol
10 (IV). This diastereomeric mixture is then separated by means known to those skilled in the art such as selective low-temperature recrystallization or chromatographic separation, most preferably by recrystallization or by employing commercially available chiral columns. The diastereomer that
15 is used in the remainder of the process of SCHEME A is the (S,S)-alcohol (IV) since this stereochemistry will give the desired epoxide (V).

The alcohol (IV) is transformed to the corresponding epoxide (V) by means known to those skilled in the art. The
20 stereochemistry of the (S)-(IV) center is maintained in forming the epoxide (V). A preferred means is by reaction with base, for example, but not limited to, hydroxide ion generated from sodium hydroxide, potassium hydroxide, lithium hydroxide and the like. Reaction conditions include the use of C₁-C₆ alcohol
25 solvents; ethanol is preferred. A common co-solvent, such as for example, ethyl acetate may also be employed. Reactions are conducted at temperatures ranging from about -45° up to the reflux temperature of the alcohol employed; preferred temperature ranges are between about -20° and about 40°.
30 The epoxide (V) is then reacted with the appropriately substituted C-terminal amine, R_C-NH₂ (VI) by means known to those skilled in the art which opens the epoxide to produce the desired corresponding enantiomerically pure (S,R)-protected alcohol (VII). The substituted C-terminal amines, R_C-NH₂ (VI)

of this invention are commercially available or are known to those skilled in the art and can be readily prepared from known compounds. It is preferred that when R_c is phenyl, it is substituted in the 3-position or 3,5-positions.

5 Suitable reaction conditions for opening the epoxide (V) include running the reaction in a wide range of common and inert solvents. C_1 - C_6 alcohol solvents are preferred and isopropyl alcohol most preferred. The reactions can be run at temperatures ranging from 20-25° up to the reflux temperature
10 of the alcohol employed. The preferred temperature range for conducting the reaction is between 50° up to the reflux temperature of the alcohol employed. When the substituted C-terminal amine (VI) is a 1-amino-3,5-cis-dimethyl cyclohexyldicarboxylate it is preferably prepared as follows.
15 To dimethyl-5-isophthalate in acetic acid and methanol, is added rhodium in alumina in a high-pressure bottle. The bottle is saturated with hydrogen at 55 psi and shaken for one week of time. The mixture is then filtered through a thick layer of celite cake and rinsed with methanol three times, the solvents
20 are removed under reduced pressure (with heat) to give a concentrate. The concentrate is triturated with ether and filtered again to give the desired C-terminal amine (VI). When the substituted C-terminal amine (VI) is 1-amino-3,5-cis-dimethoxy cyclohexane it is preferably following the general
25 procedure above and making non-critical variations but starting with 3,5-dimethoxyaniline.

When the substituted C-terminal amine (VI) is an aminomethyl group where the substituent on the methyl group is an aryl group, for example NH_2-CH_2 -aryl, is not commercially
30 available it is preferably prepared as follows. A suitable starting material is the (appropriately substituted) aralkyl compound. The first step is bromination of the alkyl substituent via methods known to those skilled in the art, see for example R.C. Larock in Comprehensive Organic

Transformations, VCH Publishers, 1989, p. 313. Next the alkyl halide is reacted with azide to produce the aryl-(alkyl)-azide. Last the azide is reduced to the corresponding amine by hydrogen/catalyst to give the C-terminal amine (VI) of formula

5 $\text{NH}_2\text{-CH}_2\text{-R}_\text{C}\text{-aryl}$.

SCHEME B discloses an alternative process for production of the enantiomerically pure (S,R)-protected alcohol (VII) from the (S)-protected compound (III). In the alternative process, the (S)-protected compound (III) is first reacted with the

10 appropriately substituted C-terminal amine $\text{R}_\text{C}\text{-NH}_2$ (VI) using the preferred conditions described above to produce the corresponding (S)-protected ketone (XI) which is then reduced using the preferred conditions described above to produce the corresponding (S,R)-protected alcohol (VII).

15 SCHEME C discloses another alternative process for production of enantiomerically pure (S,R)-protected alcohol (VII) but this time from the epoxide (V). In the process of SCHEME C, the epoxide (V) is reacted with azide to produce the corresponding enantiomerically pure (S,R)-protected azide

20 (XII). Conditions to conduct the azide mediated epoxide opening are known to those skilled in the art, see for example, J. March, Advanced Organic Chemistry, 3rd Edition, John Wiley & Sons Publishers, 1985, p. 380. Next, the (S,R)-protected azide (XII) is reduced to the corresponding protected amine (XIII) by

25 methods known to those skilled in the art. Preferred reducing conditions to reduce the (S,R)-protected azide (XII) in the presence of a t-butoxycarbonyl N-protecting group include catalytic hydrogenation, the conditions for which are known to those skilled in the art. Alternative reducing conditions

30 which may be used to avoid N-deprotection with protecting groups other than t-butoxycarbonyl are known to those skilled in the art, see for example, R.C. Larock in Comprehensive Organic Transformations, VCH Publishers, 1989, p. 409.

The (S,R)-protected alcohol (VII) is deprotected to the corresponding (S,R)-amine (VIII) by means known to those skilled in the art for removal of amine protecting group. Suitable means for removal of the amine protecting group depends on the nature of the protecting group. Those skilled in the art, knowing the nature of a specific protecting group, know which reagent is preferable for its removal. For example, it is preferred to remove the preferred protecting group, BOC, by dissolving the (S,R)-protected alcohol (VII) in a trifluoroacetic acid/dichloromethane (1/1) mixture. When complete, the solvents are removed under reduced pressure to give the corresponding (S,R)-amine (as the corresponding salt, i.e. trifluoroacetic acid salt) which is used without further purification. However, if desired, the (S,R)-amine can be purified further by means known to those skilled in the art, such as for example, recrystallization. Further, if the non-salt form is desired that also can be obtained by means known to those skilled in the art, such as for example, preparing the free base amine via treatment of the salt with mild basic conditions. Additional BOC deprotection conditions and deprotection conditions for other protecting groups can be found in T.W. Green and P.G.M. Wuts in "Protective Groups in Organic Chemistry, John Wiley and Sons, 1991, p. 309. Suitable chemically suitable salts include trifluoroacetate, and the anion of mineral acids such as chloride, sulfate, phosphate; preferred is trifluoroacetate.

The (S,R)-amine (VIII) is then reacted with an appropriately substituted amide forming agent (IX) such as, for example, an anhydride, acyl halide, or acid of the formulas $(R_N)_2O$ or R_NX or R_NOH (IX) respectively, by means known to those skilled in the art to produce the corresponding (S,R)-substituted amine X. Nitrogen acylation conditions for reaction of the (S,R)-amine (VIII) with an amide forming agent (IX) to produce the corresponding (S,R)-substituted amine X are

known to those skilled in the art and can be found in R.C. Larock in Comprehensive Organic Transformations, VCH Publishers, 1989, p. 981, 979, and 972.

5 The nitrogen-acylation of primary amines to produce secondary amides is a known reaction. Amide forming agents, $(R_N)_2O$, R_NX , and R_NOH (IX) (which are acid anhydrides, acid halides and acids respectively) are known to those skilled in the art and are commercially available or can be readily
10 prepared from known starting materials by methods known in the literature.

 SCHEME D sets forth an alternative processes for production of the (S,R)-substituted amine X from the (S,R)-protected azide (XII), which is produced from the corresponding
15 epoxide (V) in SCHEME C. The amino protecting group is removed to produce the corresponding unprotected azide (XIV) by methods previously described in SCHEME A for the conversion of (S,R)-protected alcohol (VII) to the corresponding (S,R)-amine (VIII). The (S,R)-unprotected azide (XIV) is then acylated on
20 nitrogen to produce the corresponding (S,R)-azide (XV). Next, the azide functionality is reduced as previously discussed for the conversion of the (S,R)-protected azide (XII) to the corresponding (S,R)-protected amine (XIII) to give the (S,R)-free amine (XVI). Last, the (S,R)-free amine (XVI) is
25 transformed to the corresponding (S,R)-substituted amine X by nitrogen alkylation with a compound of the formula R_C-X_3 to give the corresponding (S,R)-substituted amine X. X_3 is an appropriate leaving group, such as but not limited to, -Cl, -Br, -I, -O-mesylate, -O-tosylate, O-triflate, etc. X_3 may also
30 be an aldehyde; the corresponding coupling with (XVI) via the known reductive amination procedure gives the (S,R)-substituted amine X.

 SCHEME G discloses an alternative, and preferable, process for preparing the substituted amines X from the corresponding

protected alcohol (VII). The corresponding protected alcohol (VII) which then has the unprotected amino group protected with an amino PROTECTING GROUP, as previously discussed, to form the diprotected diamine (XXXIV). The diprotected diamine (XXXIV) has the protecting group at the N-terminal end then removed, as previously discussed, to form the monoprotected diamine (XXXV) which is then reacted with an amide forming agent (IX), as discussed above to produce the coupled product (XXXVI). Upon removal of the remaining protecting group from the coupled product (XXXVI), the desired (S,R)-substituted amine X is produced.

SCHEME H discloses a process for the preparation of a racemic amide forming agent (IX-XLI) where for R_N , R_4 is $-NH-R_4$, n_7 is 0; X is $-CH_2-$; Z is either $-SO-$ or $-SO_2-$ and ultimately the substituted amines (X-XLV) and (X-XLVI). The process of SCHEME H begins with the alcohol (XXXVII) where X_4 is C_1-C_4 alkyl or phenyl. The alcohol (XXXVII) has the alcohol group converted to a good LEAVING GROUP which includes tosylate, mesylate, nosylate and other groups known to those skilled in the art as "leaving groups" to produce the LEAVING GROUP-alcohol compound (XXXVIII). The LEAVING GROUP is replaced by the group Y-S- by reaction with a mercaptan to prepare the thiol ether (XXXIX) by means known to those skilled in the art. The thiol ether (XXXIX) is then converted to the corresponding sulfone acid (XL) by hydrolysis of the ester group. The thiol acid is then oxidized to the corresponding sulfone acid (XLI). Should it be desired that Z be $-SO-$ rather than $-SO_2-$, only one equivalent of oxidizing agent, rather than two equivalents, is used to produce the sulfoxide ($-SO-$) rather than the sulfone ($-SO_2-$) as is known to those skilled in the art. Since the remainder of the process chemistry for SCHEME H is the same regardless of whether Z is $-SO-$ or $-SO_2-$ for simplicity, only $-SO_2-$ will be illustrated and referred to. However, the

explanation is equally relevant for -SO- as is apparent to one skilled in the art. Next, the sulfone acid (XLI) is reacted with the monoprotected diamine (XXXV of SCHEME G) to produce the diprotected coupled intermediate (XLII). The diprotected coupled product (XLII) then has the PROTECTING GROUP on the R_N group (preferably BOC) selectively removed to give the monoprotected compound (XLIII). This selective removal of a PROTECTING GROUP is known to those skilled in the art and is referred to as "orthonigally protected". The monoprotected compound (XLIII) then can be selectively deprotected to give the corresponding -NH-R₄₋₁. To give the corresponding amine substituted intermediate (XLIV). The amine substituted intermediate (XLIV) is then has the remaining PROTECTING GROUP (preferably CBZ) removed by hydrogenation to give the substituted amine (X-XLV). Alternatively, the diprotected coupled intermediate (XLII) can have both PROTECTING GROUPS removed to produce the corresponding sulfone substituted amine (X-XLVI) by heating in a strong acid such as hydrochloric acid.

SCHEME I discloses a process for the preparation of enantiomerically pure thiol acid (XLIX) whereas SCHEME H disclosed a process to produce racemic thiol acid (XL). The stereoselective process of SCHEME I begins with the optically pure acid (XLVII) which is converted to the lactone (XLVIII) by Mitsunobu dehydration. The lactone (XLVII) is converted to the corresponding optically pure thiol (XLIX) by reaction of the thiol with sodium hydride in THF. The optically pure thiol (XLIX) is then oxidized as explained in SCHEME H to produce the corresponding sulfoxide (-SO-) or sulfone (-SO₂-). As with SCHEME H, only the sulfone has been carried thru by exemplification. However, the exact same process chemistry would be used to prepare the corresponding sulfoxide substituted amines (X-LIV) as was explained with regards to SCHEME H.

SCHEME J discloses a process for the preparation of substituted amines X where in the variable substituent R_N , R_4 is (III), $-(CH_2)_{1-4}-R_{4-1}$, where only one methylene group is present and R_4 is (G) giving for R_4 , $-CH_2-CO-NR_{4-3}R_{4-4}$ or (M) - $CH_2-CO-OH$. The process of SCHEME J begins with the cyclic compound (LV) which is opened by the appropriate alcohol, as is known to those skilled in the art, to give the olefin acid (LVI) where X_4 is as defined above. The olefin acid (LVI) is then transformed to the corresponding diester, preferably the activated ester (LVII) by means known to those skilled in the art. Next the Y-S- group is added to the double bond producing the thiol ester (LVIII) by Michael reaction with the appropriate thiol in methanol with triethylamine. The thiol ester (LVIII) is then converted to the corresponding acid and then reacted with the appropriate amine (VIII) to produce the protected thiol (LIX) as previously explained. This diester (LVIII) can be selectively coupled with the amine to give the protected sulfide ester (LIX). This sulfide ester (LIX) can be hydrolyzed under standard conditions (lithium hydroxide/THF/water) to give the sulfide acid (LX). Oxidation of the sulfide acid (LX) to the sulfoxide or sulfone is performed as previously stated to give the protected sulfone acid (LXI). If desired, the protected sulfone acid (LXI) can be converted to an amide by simple peptide coupling with the desired amine to give the sulfone amide (LXII). The sulfone amide (LXII) illustrates the methylamine. Simple deprotection of the R_C protecting group with an appropriate deprotecting agent is known by one skilled in the art and gives the sulfone-amide substituted amine (X-LXIII).

SCHEME K discloses an alternative and preferred process to transform the cyclic compound (LV) to the corresponding protected sulfone acid (LXI). The process of SCHEME K replaces the X_4 protecting group with a specific protecting group p-methoxybenzyl. The advantage of this group is that it, as as

the PROTECTING GROUP on the amine nitrogen, both can be removed in one step, by hydrogenation, when the PROTECTING GROUP is CBZ.

Scheme L discloses a process to prepare aminomethylene derivatives. The allylic halide (LXXI), preferably bromide, is reacted with a protected amine like phthalimide to give the N-protected amino acrylate (LXXII). The acrylate (LXXII) is reacted with the appropriate thiol, as previously described, to give the Michael product (LXXIII). Base hydrolysis of the sulfide ester (LXXIII) gives the acid (LXXIV) which is reacted with the amine (IX) as previously described to give the orthogonally protected compound (LXXV). The protecting group is removed from the protected compound (LXXV) with hydrazine to give the free amine (LXXVI) which is either acylated, X is -C(O)R to give an amide, or reacted with a mixed carbonate, X is -C(O)OR to give a carbamate (LXXVII). The sulfide (LXXVII) is oxidized as previously described to give the protected sulfone (LXXVIII). Simple de-protection of the protected sulfone (LXXVIII), as previously described, gives the target sulfone substituted amine (X-LXXIX).

Scheme M discloses the preparation of a series of racemic substituted alpha amino sulfones while Scheme N discloses the preparation of the active enantiomer. In SCHEME M, the first step discloses the Michael reaction of an appropriate thiol with a protected dehydroalanine methyl ester (LXXX) to give the thio compound (LXXXI). Oxidation as previously described gives the corresponding sulfone (LXXXII). Hydrolysis of the ester group and amino protecting group, such as acetate (-CO-CH₃) can be accomplished with strong acid, such as 6N hydrochloric acid - acetic acid at elevated temperature, to give the free amino acid hydrochloride salt (LXXXIII). Amino acid (LXXXIII) is reacted, as the free amine or salt, with the appropriate protecting group (preferably either CBZ or BOC) to give the protected amine (IX-LXXXIV). Standard peptide

coupling of the protected amine (IX-LXXXIV) preferentially gives the protected sulfone (LXXXV) which is orthogonally protected to give the diprotected sulfone (LXXXVI). Selective removal of the R_N protecting group gives the monoprotected sulfone (LXXXVII). This monoprotected sulfone (LXXXVII) can be converted as previously described, into amides, carbamates and also into ureas (by reaction of the amine with the appropriate isocyanide) and into sulfonamides by reaction with the appropriate sulfonyl chlorides. The final step is removal of the R_C protecting group to give the corresponding desired amide (X-LXXXIX). SCHEME N is identical to SCHEME M except it discloses that one can separate the isomers of (IX-LXXXIV) either by chemical, enzymatic or by chiral chromatography to yield the single isomer acid (XC) which is transformed to final product (X-XCV) as described above.

Scheme O illustrates several alcohols that can be used to prepare the carbamates of the instant invention.

Scheme P illustrates one method for preparing the compounds of the invention, starting with an enantiomerically enriched amino acid. One of ordinary skill in the art will readily recognize that the method described in Scheme P is equally as useful for preparing compounds with the opposite stereochemistry or for preparing racemic compounds.

In Scheme P, cysteine is alkylated using a base and an alkylating agent. One of ordinary skill in the art will readily recognize that other amino acids and other methods for generating the thioether can be used. The free amine is then converted into a carbamate using a chloroformate. One of skill in the art will readily recognize that the free amine may be converted into an amide, alkylated, sulfonylated, or protected rather than being converted into a carbamate. The carbamate nitrogen can optionally be alkylated using a base and an alkylating agent to generate a tertiary nitrogen. In Scheme P,

the carbamate nitrogen is alkylated with a base and an alkyl halide.

The carboxyl moiety of the starting amino acid is then reacted with an amino compound to generate the coupled compound. The amino compound can be achiral, a single enantiomer, racemic or a mixture of diastereomers. The coupled product may be further manipulated to convert the thiol into a sulfoxide, which can then be converted into a sulfone or the thiol can be directly converted into a sulfone. Other groups in the coupled product can, if desired, be manipulated using methods known in the art of organic synthesis. For example, nitrogens can be alkylated, acylated or sulfonylated. Alcohols can be converted into esters or oxidized into aldehydes or acids. Aryl groups can be acylated and halides can be coupled.

One skilled in the art will appreciate that these are all known reactions in organic chemistry. A chemist skilled in the art, knowing the chemical structure of the biologically active end product X of the invention would be able to prepare them by known methods from known starting materials without any additional information. The explanation below therefore is not necessary but is deemed helpful to those skilled in the art who desire to make the compounds of the invention.

The backbone of the compounds of the invention is a hydroxyethylamine moiety, $\text{-NH-CH(R}_1\text{)-CH(OH)-}$. It can be readily prepared by methods disclosed in the literature and known to those skilled in the art. For example, *J. Med. Chem.*, 36, 288-291 (1993), *Tetrahedron Letters*, 28, 5569-5572 (1987), *J. Med. Chem.*, 38, 581-584 (1995) and *Tetrahedron Letters*, 38, 619-620 (1997), and WO 02/02506 all disclose processes to prepare hydroxyethylamine type compounds and/or their intermediates.

The compounds of the invention may contain geometric or optical isomers as well as tautomers. Thus, the invention includes

all tautomers and pure geometric isomers, such as the *E* and *Z* geometric isomers, as mixtures thereof. Further, the invention includes pure enantiomers and diastereomers as mixtures thereof, including racemic mixtures. The individual
5 geometric isomers, enantiomers or diastereomers may be prepared or isolated by methods known to those skilled in the art, including but not limited to chiral chromatography; preparing diastereomers, separating the diastereomers and converting the diastereomers into enantiomers through the use of a chiral
10 resolving agent.

Compounds of the invention with the stereochemistry designated in formula X can be included in mixtures, including racemic mixtures, with other enantiomers, diastereomers, geometric isomers or tautomers. Compounds of the invention
15 with the (S,R) stereochemistry are typically present in these mixtures in excess of 50 percent. Preferably, compounds of the invention with the stereochemistry designated in formula X are present in these mixtures in excess of 80 percent. More preferably, compounds of the invention with the stereochemistry
20 designated in formula X are present in these mixtures in excess of 90 percent. Even more preferably, compounds of the invention with the stereochemistry designated in formula X are present in these mixtures in excess of 99 percent.

Where the compounds of formula X are amines, they form
25 salts when reacted with acids. Pharmaceutically acceptable salts are preferred over the corresponding free amines since they produce compounds which are generally more water soluble, stable and/or more crystalline. Pharmaceutically acceptable salts are any salt which retains the activity of the parent
30 compound and does not impart any deleterious or undesirable effect on the subject to whom it is administered and in the context in which it is administered. Pharmaceutically acceptable salts include salts of both inorganic and organic acids. The preferred pharmaceutically acceptable salts include

salts of the following acids acetic, aspartic, benzenesulfonic, benzoic, bicarbonic, bisulfuric, bitartaric, butyric, calcium edetate, camsylic, carbonic, chlorobenzoic, citric, edetic, edisylic, estolic, esyl, esylic, formic, fumaric, gluceptic, gluconic, glutamic, glycollylarsanilic, hexamic, hexylresorcinoic, hydrabamic, hydrobromic, hydrochloric, hydroiodic, hydroxynaphthoic, isethionic, lactic, lactobionic, maleic, malic, malonic, mandelic, methanesulfonic, methylnitric, methylsulfuric, mucic, muconic, napsylic, nitric, oxalic, p-nitromethanesulfonic, pamoic, pantothenic, phosphoric, monohydrogen phosphoric, dihydrogen phosphoric, phthalic, polygalactouronic, propionic, salicylic, stearic, succinic, succinic, sulfamic, sulfanilic, sulfonic, sulfuric, tannic, tartaric, teoclic and toluenesulfonic. For other acceptable salts, see *Int. J. Pharm.*, 33, 201-217 (1986) and *J. Pharm. Sci.*, 66(1), 1, (1977).

Inhibition of APP Cleavage

The compounds of the invention are believed to inhibit cleavage of APP between Met595 and Asp596 numbered for the APP695 isoform, or a mutant thereof, or at a corresponding site of a different isoform, such as APP751 or APP770, or a mutant thereof (sometimes referred to as the "beta secretase site". While not wishing to be bound by a particular theory, inhibition of beta-secretase activity is thought to inhibit production of beta amyloid peptide (A-beta). Inhibitory activity is demonstrated in one of a variety of inhibition assays, whereby cleavage of an APP substrate in the presence of a beta-secretase enzyme is analyzed in the presence of the inhibitory compound, under conditions normally sufficient to result in cleavage at the beta-secretase cleavage site. Reduction of APP cleavage at the beta-secretase cleavage site compared with an untreated or inactive control is correlated with inhibitory activity. Assay systems that can be used to

demonstrate efficacy of the compound inhibitors of the invention are known. Representative assay systems are described, for example, in U.S. Patents No. 5,942,400, 5,744,346, as as in the Examples below.

5 The enzymatic activity of beta-secretase and the production of A-beta can be analyzed *in vitro* or *in vivo*, using natural, mutated, and/or synthetic APP substrates, natural, mutated, and/or synthetic enzyme, and the test compound. The analysis may involve primary or secondary cells expressing
10 native, mutant, and/or synthetic APP and enzyme, or may utilize transgenic animal models expressing the substrate and enzyme. Detection of enzymatic activity can be by analysis of one or more of the cleavage products, for example, by immunoassay, flurometric or chromogenic assay, HPLC, or other means of
15 detection. Inhibitory compounds are determined as those having the ability to decrease the amount of beta-secretase cleavage product produced in comparison to a control, where beta-secretase mediated cleavage in the reaction system is observed and measured in the absence of inhibitory compounds.

20

Beta-secretase

Various forms of beta-secretase enzyme are known, and are available and useful for assay of enzyme activity and inhibition of enzyme activity. These include native,
25 recombinant, and synthetic forms of the enzyme. Human beta-secretase is known as Beta Site APP Cleaving Enzyme (BACE), Asp2, and memapsin 2, and has been characterized, for example, in U.S. Patent No. 5,744,346 and published PCT patent applications WO98/22597, WO00/03819, WO01/23533, and
30 WO00/17369, as as in literature publications (Hussain et.al., 1999, *Mol.Cell.Neurosci.* 14:419-427; Vassar et.al., 1999, *Science* 286:735-741; Yan et.al., 1999, *Nature* 402:533-537; Sinha et.al., 1999, *Nature* 40:537-540; and Lin et.al., 2000, *PNAS USA* 97:1456-1460). Synthetic forms of the enzyme have

also been described (W098/22597 and W000/17369). Beta-secretase can be extracted and purified from human brain tissue and can be produced in cells, for example mammalian cells expressing recombinant enzyme.

5 Preferred compounds are effective to inhibit 50% of beta-secretase enzymatic activity at a concentration of less than about 50 micromolar, preferably at a concentration of less than about 10 micromolar, more preferably less than about 1 micromolar, and most preferably less than about 10 nanomolar.

10

APP Substrate

Assays that demonstrate inhibition of beta-secretase-mediated cleavage of APP can utilize any of the known forms of APP, including the 695 amino acid "normal" isotype described by Kang et.al., 1987, *Nature* 325:733-6, the 770 amino acid isotype described by Kitaguchi et. al., 1981, *Nature* 331:530-532, and variants such as the Swedish Mutation (KM670-1NL) (APP-SW), the London Mutation (V7176F), and others. See, for example, U.S. Patent No. 5,766,846 and also Hardy, 1992, *Nature Genet.* 1:233-234, for a review of known variant mutations. Additional useful substrates include the dibasic amino acid modification, APP-KK disclosed, for example, in WO 00/17369, fragments of APP, and synthetic peptides containing the θ -secretase cleavage site, wild type (WT) or mutated form, e.g., SW, as described, for example, in U.S. Patent No 5,942,400 and W000/03819.

The APP substrate contains the beta-secretase cleavage site of APP (KM-DA or NL-DA) for example, a complete APP peptide or variant, an APP fragment, a recombinant or synthetic APP, or a fusion peptide. Preferably, the fusion peptide includes the beta-secretase cleavage site fused to a peptide having a moiety useful for enzymatic assay, for example, having isolation and/or detection properties. A useful moiety may be an antigenic epitope for antibody binding, a label or other detection moiety, a binding substrate, and the like.

Antibodies

Products characteristic of APP cleavage can be measured by immunoassay using various antibodies, as described, for example, in Pirttila et.al., 1999, *Neuro.Lett.* 249:21-4, and in U.S. Patent No. 5,612,486. Useful antibodies to detect A-beta include, for example, the monoclonal antibody 6E10 (Senetek, St. Louis, MO) that specifically recognizes an epitope on amino acids 1-16 of the A-beta peptide; antibodies 162 and 164 (New York State Institute for Basic Research, Staten Island, NY) that are specific for human A-beta 1-40 and 1-42, respectively; and antibodies that recognize the junction region of beta-amyloid peptide, the site between residues 16 and 17, as described in U.S. Patent No. 5,593,846. Antibodies raised against a synthetic peptide of residues 591 to 596 of APP and SW192 antibody raised against 590-596 of the Swedish mutation are also useful in immunoassay of APP and its cleavage products, as described in U.S. Patent Nos. 5,604,102 and 5,721,130.

Assay Systems

Assays for determining APP cleavage at the beta-secretase cleavage site are known in the art. Exemplary assays, are described, for example, in U.S. Patent Nos. 5,744,346 and 5,942,400, and described in the Examples below.

Cell Free Assays

Exemplary assays that can be used to demonstrate the inhibitory activity of the compounds of the invention are described, for example, in WO00/17369, WO 00/03819, and U.S. Patents No. 5,942,400 and 5,744,346. Such assays can be performed in cell-free incubations or in cellular incubations using cells expressing a beta-secretase and an APP substrate having a beta-secretase cleavage site.

An APP substrate containing the beta-secretase cleavage site of APP, for example, a complete APP or variant, an APP fragment, or a recombinant or synthetic APP substrate containing the amino acid sequence: KM-DA or NL-DA, is incubated in the presence of beta-secretase enzyme, a fragment thereof, or a synthetic or recombinant polypeptide variant having beta-secretase activity and effective to cleave the beta-secretase cleavage site of APP, under incubation conditions suitable for the cleavage of the enzyme. Suitable substrates optionally include derivatives that may be fusion proteins or peptides that contain the substrate peptide and a modification useful to facilitate the purification or detection of the peptide or its beta-secretase cleavage products. Useful modifications include the insertion of a known antigenic epitope for antibody binding; the linking of a label or detectable moiety, the linking of a binding substrate, and the like.

Suitable incubation conditions for a cell-free in vitro assay include, for example: approximately 200 nanomolar to 10 micromolar substrate, approximately 10 to 200 picomolar enzyme, and approximately 0.1 nanomolar to 10 micromolar inhibitor compound, in aqueous solution, at an approximate pH of 4 -7, at approximately 37 degrees C, for a time period of approximately 10 minutes to 3 hours. These incubation conditions are exemplary only, and can be varied as required for the particular assay components and/or desired measurement system. Optimization of the incubation conditions for the particular assay components should account for the specific beta-secretase enzyme used and its pH optimum, any additional enzymes and/or markers that might be used in the assay, and the like. Such optimization is routine and will not require undue experimentation.

One useful assay utilizes a fusion peptide having maltose binding protein (MBP) fused to the C-terminal 125 amino acids

of APP-SW. The MBP portion is captured on an assay substrate by anti-MBP capture antibody. Incubation of the captured fusion protein in the presence of beta-secretase results in cleavage of the substrate at the beta-secretase cleavage site.

5 Analysis of the cleavage activity can be, for example, by immunoassay of cleavage products. One such immunoassay detects a unique epitope exposed at the carboxy terminus of the cleaved fusion protein, for example, using the antibody SW192. This assay is described, for example, in U.S. Patent No 5,942,400.

10

Cellular Assay

Numerous cell-based assays can be used to analyze beta-secretase activity and/or processing of APP to release A-beta. Contact of an APP substrate with a beta-secretase enzyme within
15 the cell and in the presence or absence of a compound inhibitor of the invention can be used to demonstrate beta-secretase inhibitory activity of the compound. Preferably, assay in the presence of a useful inhibitory compound provides at least about 30%, most preferably at least about 50% inhibition of the
20 enzymatic activity, as compared with a non-inhibited control.

In one embodiment, cells that naturally express beta-secretase are used. Alternatively, cells are modified to express a recombinant beta-secretase or synthetic variant enzyme as discussed above. The APP substrate may be added to
25 the culture medium is preferably expressed in the cells. Cells that naturally express APP, variant or mutant forms of APP, or cells transformed to express an isoform of APP, mutant or variant APP, recombinant or synthetic APP, APP fragment, or synthetic APP peptide or fusion protein containing the beta-secretase APP cleavage site can be used, provided that the
30 expressed APP is permitted to contact the enzyme and enzymatic cleavage activity can be analyzed.

Human cell lines that normally process A-beta from APP provide a useful means to assay inhibitory activities of the

compounds of the invention. Production and release of A-beta and/or other cleavage products into the culture medium can be measured, for example by immunoassay, such as Western blot or enzyme-linked immunoassay (EIA) such as by ELISA.

5 Cells expressing an APP substrate and an active beta-secretase can be incubated in the presence of a compound inhibitor to demonstrate inhibition of enzymatic activity as compared with a control. Activity of beta-secretase can be measured by analysis of one or more cleavage products of the
10 APP substrate. For example, inhibition of beta-secretase activity against the substrate APP would be expected to decrease release of specific beta-secretase induced APP cleavage products such as A-beta.

 Although both neural and non-neural cells process and
15 release A-beta, levels of endogenous beta-secretase activity are low and often difficult to detect by EIA. The use of cell types known to have enhanced beta-secretase activity, enhanced processing of APP to A-beta, and/or enhanced production of A-beta are therefore preferred. For example, transfection of
20 cells with the Swedish Mutant form of APP (APP-SW); with APP-KK; or with APP-SW-KK provides cells having enhanced β -secretase activity and producing amounts of A-beta that can be readily measured.

 In such assays, for example, the cells expressing APP and
25 beta-secretase are incubated in a culture medium under conditions suitable for beta-secretase enzymatic activity at its cleavage site on the APP substrate. On exposure of the cells to the compound inhibitor, the amount of A-beta released into the medium and/or the amount of CTF99 fragments of APP in
30 the cell lysates is reduced as compared with the control. The cleavage products of APP can be analyzed, for example, by immune reactions with specific antibodies, as discussed above.

 Preferred cells for analysis of beta-secretase activity include primary human neuronal cells, primary transgenic animal

neuronal cells where the transgene is APP, and other cells such as those of a stable 293 cell line expressing APP, for example, APP-SW.

5 **In vivo Assays: Animal Models**

Various animal models can be used to analyze beta-secretase activity and /or processing of APP to release A-beta, as described above. For example, transgenic animals expressing APP substrate and beta-secretase enzyme can be used to demonstrate inhibitory activity of the compounds of the invention. Certain transgenic animal models have been described, for example, in U.S. Patent Nos: 5,877,399; 5,612,486; 5,387,742; 5,720,936; 5,850,003; 5,877,015,, and 5,811,633, and in Ganes et.al., 1995, *Nature* 373:523. Preferred are animals that exhibit characteristics associated with the pathophysiology of AD. Administration of the compound inhibitors of the invention to the transgenic mice described herein provides an alternative method for demonstrating the inhibitory activity of the compounds. Administration of the compounds in a pharmaceutically effective carrier and via an administrative route that reaches the target tissue in an appropriate therapeutic amount is also preferred.

Inhibition of beta-secretase mediated cleavage of APP at the beta-secretase cleavage site and of A-beta release can be analyzed in these animals by measure of cleavage fragments in the animal's body fluids such as cerebral fluid or tissues. Analysis of brain tissues for A-beta deposits or plaques is preferred.

On contacting an APP substrate with a beta-secretase enzyme in the presence of an inhibitory compound of the invention and under conditions sufficient to permit enzymatic mediated cleavage of APP and/or release of A-beta from the substrate, the compounds of the invention are effective to reduce β -secretase-mediated cleavage of APP at the beta-

secretase cleavage site and/or effective to reduce released amounts of A-beta. Where such contacting is the administration of the inhibitory compounds of the invention to an animal model, for example, as described above, the compounds are effective to reduce A-beta deposition in brain tissues of the animal, and to reduce the number and/or size of beta amyloid plaques. Where such administration is to a human subject, the compounds are effective to inhibit or slow the progression of disease characterized by enhanced amounts of A-beta, to slow the progression of AD in the, and/or to prevent onset or development of AD in a patient at risk for the disease.

Unless defined otherwise, all scientific and technical terms used herein have the same meaning as commonly understood by one of skill in the art to which this invention belongs. All patents and publications referred to herein are hereby incorporated by reference for all purposes.

Biology Examples

Example A

Enzyme inhibition assay

The compounds of the invention are analyzed for inhibitory activity by use of the MBP-C125 assay. This assay determines the relative inhibition of beta-secretase cleavage of a model APP substrate, MBP-C125SW, by the compounds assayed as compared with an untreated control. A detailed description of the assay parameters can be found, for example, in U.S. Patent No. 5,942,400. Briefly, the substrate is a fusion peptide formed of maltose binding protein (MBP) and the carboxy terminal 125 amino acids of APP-SW, the Swedish mutation. The beta-secretase enzyme is derived from human brain tissue as described in Sinha et.al, 1999, Nature 40:537-540) or recombinantly produced as the full-length enzyme (amino acids 1-501), and can be prepared, for example, from 293 cells expressing the recombinant cDNA, as described in WO00/47618.

Inhibition of the enzyme is analyzed, for example, by immunoassay of the enzyme's cleavage products. One exemplary ELISA uses an anti-MBP capture antibody that is deposited on precoated and blocked 96- high binding plates, followed by
5 incubation with diluted enzyme reaction supernatant, incubation with a specific reporter antibody, for example, biotinylated anti-SW192 reporter antibody, and further incubation with streptavidin/alkaline phosphatase. In the assay, cleavage of the intact MBP-C125SW fusion protein results in the generation
10 of a truncated amino-terminal fragment, exposing a new SW-192 antibody-positive epitope at the carboxy terminus. Detection is effected by a fluorescent substrate signal on cleavage by the phosphatase. ELISA only detects cleavage following Leu 596 at the substrate's APP-SW 751 mutation site.

15 **Specific Assay Procedure**

Compounds are diluted in a 1:1 dilution series to a six-point concentration curve (two wells per concentration) in one 96-plate row per compound tested. Each of the test compounds is prepared in DMSO to make up a 10 millimolar stock solution.
20 The stock solution is serially diluted in DMSO to obtain a final compound concentration of 200 micromolar at the high point of a 6-point dilution curve. Ten (10) microliters of each dilution is added to each of two wells on row C of a corresponding V-bottom plate to which 190 microliters of 52
25 millimolar NaOAc, 7.9% DMSO, pH 4.5 are pre-added. The NaOAc diluted compound plate is spun down to pellet precipitant and 20 microliters/well is transferred to a corresponding flat-bottom plate to which 30 microliters of ice-cold enzyme-substrate mixture (2.5 microliters MBP-C125SW substrate, 0.03
30 microliters enzyme and 24.5 microliters ice cold 0.09% TX100 per 30 microliters) is added. The final reaction mixture of 200 micromolar compound at the highest curve point is in 5% DMSO, 20 millimolar NaAc, 0.06% TX100, at pH 4.5.

Warming the plates to 37 degrees C starts the enzyme reaction. After 90 minutes at 37 degrees C, 200 microliters/ cold specimen diluent is added to stop the reaction and 20 microliters/ was transferred to a corresponding anti-MBP
5 antibody coated ELISA plate for capture, containing 80 microliters/ specimen diluent. This reaction is incubated overnight at 4 degrees C and the ELISA is developed the next day after a 2 hour incubation with anti-192SW antibody, followed by Streptavidin-AP conjugate and fluorescent
10 substrate. The signal is read on a fluorescent plate reader.

Relative compound inhibition potency is determined by calculating the concentration of compound that showed a fifty-percent reduction in detected signal (IC_{50}) compared to the enzyme reaction signal in the control s with no added compound.
15 In this assay, the compounds of the invention exhibited an IC_{50} of less than 50 micromolar.

Example B

Cell free inhibition assay utilizing a synthetic APP 20 substrate

A synthetic APP substrate that can be cleaved by beta-secretase and having N-terminal biotin and made fluorescent by the covalent attachment of oregon green at the Cys residue is used to assay beta-secretase activity in the presence or
25 absence of the inhibitory compounds of the invention. Useful substrates include the following:

Biotin-SEVNL-DAEFRC[oregon green]KK [SEQ ID NO: 1]
Biotin-SEVKM-DAEFRC[oregon green]KK [SEQ ID NO: 2]
30 Biotin-GLNIKTEEISEISY-EVEFRC[oregon green]KK [SEQ ID NO: 3]
Biotin-ADRGLTTRPGSGLTNIKTEEISEVNL-DAEFRC[oregon green]KK [SEQ ID NO: 4]
Biotin-FVNQHLCoxGSHLVEALY-LVCoxGERGFFYTPKAC[oregon green]KK
[SEQ ID NO: 5]

The enzyme (0.1 nanomolar) and test compounds (0.001 - 100 micromolar) are incubated in pre-blocked, low affinity, black plates (384) at 37 degrees for 30 minutes. The reaction is initiated by addition of 150 millimolar substrate to a final
5 volume of 30 microliter per . The final assay conditions are: 0.001 - 100 micromolar compound inhibitor; 0.1 molar sodium acetate (pH 4.5); 150 nanomolar substrate; 0.1 nanomolar soluble beta-secretase; 0.001% Tween 20, and 2% DMSO. The assay mixture is incubated for 3 hours at 37 °C, and the
10 reaction is terminated by the addition of a saturating concentration of immunopure streptavidin. After incubation with streptavidin at room temperature for 15 minutes, fluorescence polarization is measured, for example, using a LJL Acquest (Ex485 nm/ Em530 nm). The activity of the beta-
15 secretase enzyme is detected by changes in the fluorescence polarization that occur when the substrate is cleaved by the enzyme. Incubation in the presence or absence of compound inhibitor demonstrates specific inhibition of beta-secretase enzymatic cleavage of its synthetic APP substrate. In this
20 assay, compounds of the invention exhibited an IC50 of less than 50 micromolar.

Example C

Beta-secretase inhibition: P26-P4'SW assay

Synthetic substrates containing the θ -secretase cleavage site of APP are used to assay beta-secretase activity, using the methods described, for example, in published PCT application WO00/47618. The P26-P4'SW substrate is a peptide of the sequence: (biotin)CGGADRGLTTRPGSGLTNIKTEEISEVNLD AEF

[SEQ ID NO: 6]

The P26-P1 standard has the sequence:

10 (biotin)CGGADRGLTTRPGSGLTNIKTEEISEVNL [SEQ ID NO: 7]

Briefly, the biotin-coupled synthetic substrates are incubated at a concentration of from about 0 to about 200 micromolar in this assay. When testing inhibitory compounds, a substrate concentration of about 1.0 micromolar is preferred.

15 Test compounds diluted in DMSO are added to the reaction mixture, with a final DMSO concentration of 5%. Controls also contain a final DMSO concentration of 5%. The concentration of beta secretase enzyme in the reaction is varied, to give product concentrations with the linear range of the ELISA assay, about 125 to 2000 picomolar, after dilution.

The reaction mixture also includes 20 millimolar sodium acetate, pH 4.5, 0.06% Triton X100, and is incubated at 37 degrees C for about 1 to 3 hours. Samples are then diluted in assay buffer (for example, 145.4 nanomolar sodium chloride, 9.51 millimolar sodium phosphate, 7.7 millimolar sodium azide, 0.05% Triton X405, 6g/liter bovine serum albumin, pH 7.4) to quench the reaction, then diluted further for immunoassay of the cleavage products.

Cleavage products can be assayed by ELISA. Diluted samples and standards are incubated in assay plates coated with capture antibody, for example, SW192, for about 24 hours at 4 degrees C. After washing in TTBS buffer (150 millimolar sodium chloride, 25 millimolar Tris, 0.05% Tween 20, pH 7.5), the samples are incubated with strepavidin-AP according to the

manufacturer's instructions. After a one hour incubation at room temperature, the samples are washed in TTBS and incubated with fluorescent substrate solution A (31.2 g/liter 2-amino-2-methyl-1-propanol, 30 mg/liter, pH 9.5). Reaction with streptavidin-alkaline phosphate permits detection by fluorescence. Compounds that are effective inhibitors of θ -secretase activity demonstrate reduced cleavage of the substrate as compared to a control.

Example D

Assays using synthetic oligopeptide-substrates

Synthetic oligopeptides are prepared that incorporate the known cleavage site of beta-secretase, and optionally detectable tags, such as fluorescent or chromogenic moieties. Examples of such peptides, as well as their production and detection methods are described in U.S. Patent No: 5,942,400, herein incorporated by reference. Cleavage products can be detected using high performance liquid chromatography, or fluorescent or chromogenic detection methods appropriate to the peptide to be detected, according to methods known in the art.

By way of example, one such peptide has the sequence SEVNL-DAEF [SEQ ID NO: 8], and the cleavage site is between residues 5 and 6. Another preferred substrate has the sequence ADRGLTTRPGSGLTNIKTEEISEVNL-DAEF [SEQ ID NO: 9], and the cleavage site is between residues 26 and 27.

These synthetic APP substrates are incubated in the presence of beta-secretase under conditions sufficient to result in beta-secretase mediated cleavage of the substrate. Comparison of the cleavage results in the presence of the compound inhibitor to control results provides a measure of the compound's inhibitory activity.

Example E

Inhibition of beta-secretase activity-cellular assay

An exemplary assay for the analysis of inhibition of beta-secretase activity utilizes the human embryonic kidney cell line HEKp293 (ATCC Accession No. CRL-1573) transfected with APP751 containing the naturally occurring double mutation
5 Lys651Met52 to Asn651Leu652 (numbered for APP751), commonly called the Swedish mutation and shown to overproduce A-beta (Citron et.al., 1992, Nature 360:672-674), as described in USPN 5,604,102.

The cells are incubated in the presence/absence of the
10 inhibitory compound (diluted in DMSO) at the desired concentration, generally up to 10 micrograms/ml. At the end of the treatment period, conditioned media is analyzed for beta-secretase activity, for example, by analysis of cleavage fragments. A-beta can be analyzed by immunoassay, using
15 specific detection antibodies. The enzymatic activity is measured in the presence and absence of the compound inhibitors to demonstrate specific inhibition of beta-secretase mediated cleavage of APP substrate.

20 **Example F**

Inhibition of beta-secretase in animal models of AD

Various animal models can be used to screen for inhibition of beta-secretase activity. Examples of animal models useful in the invention include, but are not limited to, mouse, guinea
25 pig, dog, and the like. The animals used can be wild type, transgenic, or knockout models. In addition, mammalian models can express mutations in APP, such as APP695-SW and the like described herein. Examples of transgenic non-human mammalian models are described in U.S. Patent Nos. 5,604,102, 5,912,410
30 and 5,811,633.

PDAPP mice, prepared as described in Games et.al., 1995, Nature 373:523-527 are useful to analyze in vivo suppression of A-beta release in the presence of putative inhibitory compounds. As described in USPN 6,191,166, 4 month old PDAPP

mice are administered compound formulated in vehicle, such as corn oil. The mice are dosed with compound (1-30 mg/ml; preferably 1-10 mg/ml). After time, e.g., 3-10 hours, the animals are sacrificed, and brains removed for analysis.

5 Transgenic animals are administered an amount of the compound inhibitor formulated in a carrier suitable for the chosen mode of administration. Control animals are untreated, treated with vehicle, or treated with an inactive compound. Administration can be acute, i.e., single dose or multiple
10 doses in one day, or can be chronic, i.e., dosing is repeated daily for a period of days. Beginning at time 0, brain tissue or cerebral fluid is obtained from selected animals and analyzed for the presence of APP cleavage peptides, including A-beta, for example, by immunoassay using specific antibodies
15 for A-beta detection. At the end of the test period, animals are sacrificed and brain tissue or cerebral fluid is analyzed for the presence of A-beta and/or beta-amyloid plaques. The tissue is also analyzed for necrosis.

Animals administered the compound inhibitors of the
20 invention are expected to demonstrate reduced A-beta in brain tissues or cerebral fluids and reduced beta amyloid plaques in brain tissue, as compared with non-treated controls.

Example G

Inhibition of A-beta production in human patients

Patients suffering from Alzheimer's Disease (AD) demonstrate an increased amount of A-beta in the brain. AD patients are administered an amount of the compound inhibitor formulated in a carrier suitable for the chosen mode of administration. Administration is repeated daily for the duration of the test period. Beginning on day 0, cognitive and memory tests are performed, for example, once per month.

Patients administered the compound inhibitors are expected to demonstrate slowing or stabilization of disease progression as analyzed by changes in one or more of the following disease parameters: A-beta present in CSF or plasma; brain or hippocampal volume; A-beta deposits in the brain; amyloid plaque in the brain; and scores for cognitive and memory function, as compared with control, non-treated patients.

Example H

Prevention of A-beta production in patients at risk for AD

Patients predisposed or at risk for developing AD are identified either by recognition of a familial inheritance pattern, for example, presence of the Swedish Mutation, and/or by monitoring diagnostic parameters. Patients identified as predisposed or at risk for developing AD are administered an amount of the compound inhibitor formulated in a carrier suitable for the chosen mode of administration. Administration is repeated daily for the duration of the test period. Beginning on day 0, cognitive and memory tests are performed, for example, once per month.

Patients administered the compound inhibitors are expected to demonstrate slowing or stabilization of disease progression as analyzed by changes in one or more of the following disease parameters: A-beta present in CSF or plasma; brain or hippocampal volume; amyloid plaque in the brain; and scores

for cognitive and memory function, as compared with control, non-treated patients.

EXAMPLES

5 The following detailed examples describe how to prepare the various compounds and/or perform the various processes of the invention and are to be construed as merely illustrative, and not limitations of the preceding disclosure in any way whatsoever. Those skilled in the art will promptly recognize
10 appropriate variations from the procedures both as to reactants and as to reaction conditions and techniques.

PREPARATION 1 tert-Butyl (1S)-3-bromo-1-(3,5-difluorobenzyl)-
2-oxopropylcarbamate (III)

15 N-methyl-morpholine (5.83 mL, 53 mmole, 1.05 eq.) is added to (2S)-2-[(tert-butoxycarbonyl)amino]-3-(3,5-difluorophenyl)propanoic acid (II, 15 g, 50 mmole) in THF (100 mL) and the reaction is cooled to -78°. Isobutyl chloroformate (6.87 mL, 53 mmole, 1.05 eq.) is added rapidly. The cold bath
20 is then removed and the mixture stirred for 1 hr. The reaction was monitored by TLC to insure completion of the reaction and the mixture is then filtered and washed with dry THF (50 mL) and kept cold in the filtered flask at -20°.

 In a ice-salt bath is placed a 500 mL graduate cylinder
25 containing ether (200 mL) and aqueous potassium hydroxide (40%, 60 mL). 1-methyl-3-nitro-1-nitrosoguanidine (5.6 g, 106 mmole, 2.1 eq.) is added slowly with stirring and temperature kept below zero degree. The mixture turned yellow and the bubbling lasted for 10 minutes. The stirring is stopped and without
30 mixing the layers, the top diazomethane ethereal layer is transferred with non-ground tip pipette into the stirred mixed anhydride mixture at -20°. The reaction is monitored by TLC (ethyl acetate/hexane, 50/50; R_f = 0.69). After 1 hour nitrogen is then bubbled into the mixture. The solvent is

removed under reduced pressure (with heat) and the mixture is partitioned between ether and water. The phases are separated, the organic phase is washed with bicarbonate, saline, dried over anhydrous sodium sulfate, filtered, and solvent removed under reduced pressure (with heat). The residue is dissolved in ether (100 mL) and hydrobromous acid (48%, 15 mL, 135 mmole, 2.7 eq.) is added at -20°, the cold bath is removed and the mixture is stirred for another half hour. The reaction is monitored by TLC (ethyl acetate/hexane, 50/50; R_f = 0.88). The mixture is partitioned between ether and water, washed with bicarbonate, saline, dried over anhydrous sodium sulfate, filtered, and the solvent removed. The residue is recrystallized from ethanol to give the title compound, TLC (ethyl acetate/hexane, 50/50) R_f = 0.88; MS (MH^+) = 379.3

PREPARATION 2 tert-Butyl (1S, 2S)-3-bromo-1-(3,5-difluorobenzyl)-2-hydroxypropylcarbamate (IV)

Sodium borohydride (1.32 g, 34.9 mmole, 1.1 eq.) is added to tert-Butyl (1S)-3-bromo-1-(3,5-difluorobenzyl)-2-oxopropylcarbamate (III, PREPARATION 1, 12 g, 31.75 mmole) dissolved in absolute alcohol (500 mL) -78°. The reaction mixture is stirred for 30 minutes and monitored by TLC (ethyl acetate/hexane, 20/80; R_f = 0.2). The mixture is quenched with water (10 mL) and the solvent removed under reduced pressure with heat (not exceeding 30°) to dryness. The solid is partitioned between dichloromethane and water, washed with saline, dried over anhydrous sodium sulfate. The solvent is removed under reduced pressure to give the title compound, TLC (ethyl acetate/hexane, 20/80) R_f = 0.2; MS (MH^+) = 381.2

PREPARATION 3 tert-Butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiranyl]ethylcarbamate (V)

tert-Butyl (1S, 2S)-3-bromo-1-(3,5-difluorobenzyl)-2-hydroxypropylcarbamate (IV, PREPARATION 2) is dissolved in

absolute alcohol (150 mL) and ethyl acetate (100 mL) and potassium hydroxide (2.3 g, 34.9 mmole, 1.1eq.) in ethyl alcohol (85%, 5mL) is added at -20°. The cold bath is then removed and the mixture stirred for 30 minutes. The reaction
5 is monitored by TLC (ethyl acetate/hexane, 20/80). When the reaction is complete, it is diluted with dichloromethane and extracted, washed with water, saline, dried over anhydrous sodium sulfate and the solvent removed under reduced pressure. The crude material is purified by flash chromatography on
10 silica gel to give the title compound, TLC (ethyl acetate/hexane, 20/80) $R_f = 0.3$; MS (MH^+) = 300.4.

PREPARATION 4 Benzyl (1S)-3-chloro-1-(3,5-difluorobenzyl)-2-oxopropylcarbamate (III)

15 Following the general procedure of PREPARATION 1 and making non critical variations but starting with the CBZ protecting group and using hydrochloric acid, the title compound is obtained.

20 PREPARATION 5 Benzyl (1S, 2S)-3-chloro-1-(3,5-difluorobenzyl)-2-hydroxypropylcarbamate (IV)

Following the general procedure of PREPARATION 2 and making non critical variations but starting with benzyl (1S)-3-chloro-1-(3,5-difluorobenzyl)-2-oxopropylcarbamate (III,
25 PREPARATION 4), the title compound is obtained.

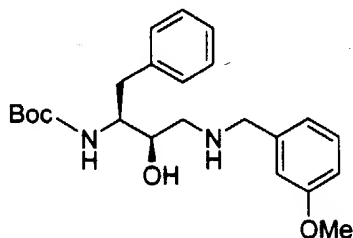
PREPARATION 6 Benzyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiranyl]ethylcarbamate (V)

Following the general procedure of PREPARATION 3 and
30 making non critical variations but starting with benzyl (1S, 2S)-3-chloro-1-(3,5-difluorobenzyl)-2-hydroxypropylcarbamate (IV, PREPARATION 5), the title compound is obtained.

PREPARATION 7 tert-Butyl (1S, 2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propylcarbamate (VII)

tert-Butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxirany]ethylcarbamate (V, PREPARATION 3, 245 mg, 0.82 mmol) is suspended in isopropyl alcohol (6 mL) and 3-methoxybenzylamine (160 μ L, 1.22 mmol) is added with stirring at 20-25°. This mixture is heated to gentle reflux (bath temp 85°) under nitrogen for 2 hr, whereupon the resulting mixture is concentrated under reduced pressure to give the title compound. The title compound is purified by flash chromatography (2-5% methanol/methylene chloride; gradient elution) to give purified title compound.

PREPARATION 8 tert-Butyl (1S, 2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propylcarbamate (VII)



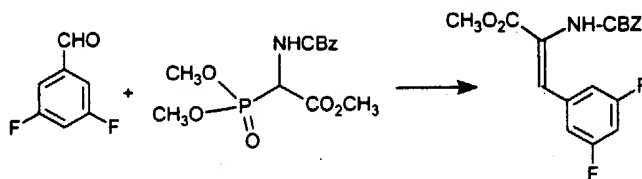
tert-Butyl 1-(2-oxiranyl)-2-phenylethylcarbamate (V, commercially available, 20 g, 76 mmole) is dissolved in i-propanol (380 ml). To this mixture is added 3-methoxybenzylamine (49 ml, 380 mmole). The reaction mixture is heated to reflux for 1 hr (when HPLC indicated complete reaction). The reaction mixture is concentrated under reduced pressure and the residue is treated with hexane (500 ml). The product is isolated by filtration. The mother liquors are concentrated under reduced pressure to give additional crude material which is partitioned between ethyl acetate (50 ml) and water (50 ml). The mixture is acidified with concentrated hydrochloric acid (to pH = 4), the organic phase is separated and washed with

water, saline, dried over sodium sulfate and then concentrated under reduced pressure to give additional title compound, M+H = 401.

5 PREPARATION 9 Benzyl (1S, 2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]ethyl carbamate (VII)

Following the general procedure of PREPARATION 7 and making non-critical variations but using benzyl 1-(2-oxiranyl)-2-phenyl carbamate (V), as the epoxide, the title compound is
10 obtained.

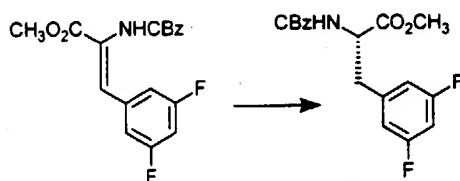
PREPARATION 10 Methyl (2Z)-2-[[[(benzyloxy)carbonyl]-3-(3,5-difluorophenyl)-2-propenonate (XXII)



15 3,5-Difluorobenzaldehyde (XX, 2.87 g, 0.02 moles, 1 eq) and THF (100 mL) are mixed and cooled to about 0°. N-(Benzyloxycarbonyl)phosphonyl-glycinetrimethylester (XXI, 8.7 g, 0.026 moles, 1.3 eq) is added to the 3,5-difluorobenzaldehyde (XX)/THF mixture. This is followed by
20 1,1,3,3-tetramethyl guanidine (4.0 mL, 0.032 moles, 1.56 eq) added dropwise. The reaction is stirred for 5 min at 0° then allowed to warm to 20-25°. After 2 hr, the reaction is complete (by TLC analysis) at which time water (100 mL) and ethyl acetate (100 mL) are added. The phases are separated and
25 the aqueous phase is extracted with ethyl acetate (100 mL) and the combined organic phases are washed with saline (100 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to give a crude solid. The solid is purified by silica gel chromatography (ethyl acetate/hexanes; 15/85) to
30 give the title compound, mp = 112°; NMR (CDCl₃) δ 7.19, 7.06,

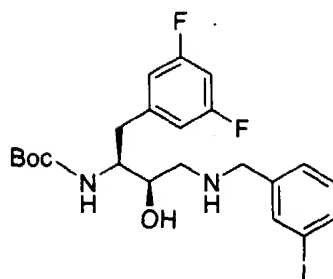
6.86, 6.15, 6.43, 4.97 and 3.69; CMR (CDCl₃) δ 165.56, 164.54, 164.41, 162.07, 137.39, 136.02, 128.97, 128.80, 128.62, 128.57, 128.47, 126.25, 112.57, 112.38, 105.22, 104.97, 104.72, 68.17 and 53.33. Additional material is recovered that is a mixture
5 of E and Z olefins.

PREPARATION 11 methyl (2S)-2-[[(benzyloxy)carbonyl]amino]-3-(3,5-difluorophenyl)propanoate (II)



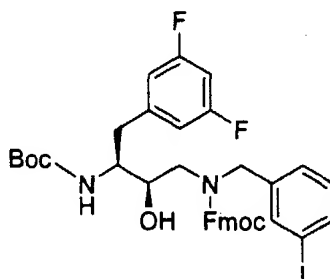
10 Methyl (2Z)-2-[[(benzyloxy)carbonyl]-3-(3,5-difluorophenyl)-2-propenonate (XXII, PREPARATION 10, 0.100 g, 0.228 mmol) and degassed methanol (10 ml) are mixed in a 100 mL Hastelloy bomb. The reaction mixture is purged three times with
15 hydrogen (60 psig) and then stirred at 60 psig hydrogen for 60 min at 20-25°. Then (R,R)-DIPAPRh (5.2 mg, 3 mole%) is dissolved in methanol (1 mL, degassed) is added and the system purged with hydrogen (3 x 60 psig). The contents are then stirred at 20 psig hydrogen at 25° overnight at which time the
20 reaction is complete as determined by HPLC. The system is then purged and filtered to remove the catalyst and the solvent is removed under reduced pressure to give the title compound.

PREPARATION 12 1- tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propylcarbamate (VII)



tert-Butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-
oxirany]ethylcarbamate (V, PREPARATION 3, 1.75 g, 5.8 mmole)
5 is mixed with isopropanol (30 ml). The reaction flask is
charged with 3-iodobenzylamine (VI). The reaction mixture is
heated to reflux for 45 minutes, HPLC analysis indicates
complete disappearance of the epoxide (V). The reaction
mixture is concentrated under reduced pressure and the residue
10 is partitioned between ethyl acetate (150 ml) and aqueous
hydrochloric acid (3%, 35 ml). The organic phase is separated
and washed with aqueous hydrochloric acid (3%, 20 ml),
bicarbonate, saline and dried over sodium sulfate.
Concentration under reduced pressure gives the title compound,
15 M + H = 535.

PREPARATION 13 1-9H-fluoren-9-ylmethyl (2R,3S)-3-(3-t-
butyloxycarbonyl)amino-4-(3,5-difluorophenyl)-2-
hydroxybutyl(3'-iodobenzyl)carbamate hydrochloride (XXXIV)

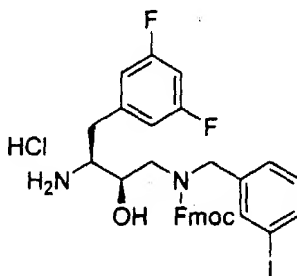


1- tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-
[(3-iodobenzyl)amino]propylcarbamate (VII, PREPARATION 12, 2.5

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PHA No. 00-530.US1 Elan No. 530-US

g, 4.7 mmole) and triethylamine (0.72 ml, 5.1 mmole) in THF (10 ml) are mixed. The reaction is cooled to 0° and treated with Fmoc (1.2 g, 4.7 mmole) in THF (2 ml) via addition funnel. After 15 minutes HPLC indicates complete
5 disappearance of starting material. The reaction is diluted with ethyl acetate and washed with aqueous potassium bisulfate, saturated aqueous bicarbonate, saline and dried over sodium sulfate. Concentration under reduced pressure gives crude product which is purified by flash chromatography,
10 eluting with ethyl acetate/hexane (20/80) followed by ethyl acetate to give the title compound, M + H = 757.

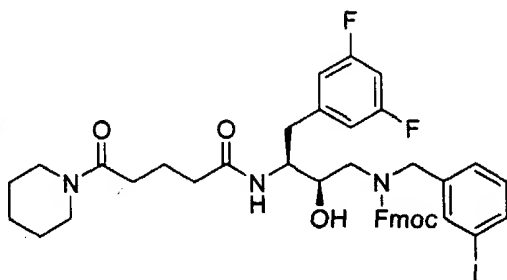
PREPARATION 14 1-9H-fluoren-9-ylmethyl (2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl(3-iodobenzyl)carbamate
15 hydrochloride (XXXV)



1-9H-fluoren-9-ylmethyl (2R,3S)-3-(3-t-
20 butyloxycarbonyl)amino-4-(3,5-difluorophenyl)-2-hydroxybutyl(3'-iodobenzyl)carbamate hydrochloride (XXXIV, PREPARATION 13, 2.9 g) in hydrochloric acid/dioxane (4N, 10 ml). The mixture is stirred 1 hour then slowly poured into rapidly stirring ether (200 ml). The product is filtered and
25 dried to give the title compound, M + H = 657.

PREPARATION 15 1-9H-fluoren-9-ylmethyl (2R,3S)-4-(3,5-difluorophenyl)-2-hydroxy-3-[[5-oxo-5-(1-

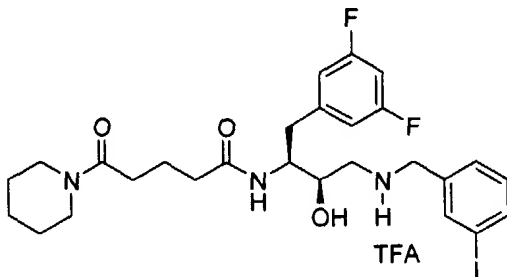
piperidiny]pentanoyl]amino}butyl(3-iodobenzyl)carbamate
(XXXVI)



5 HOBt (81 mg, 0.6 mmole) and EDC (105 mg, 0.55 mmole) are added to 1-carboxy-5-piperdiny]glutaramide (IX, 100 mg, 0.5 mmole) in DMF (2 ml). The acid is activated 60 minutes then treated with 1-9H-fluoren-9-ylmethyl (2R,3S)-3-amino-4-(3,5-difluorophenyl)-2-hydroxybutyl(3-iodobenzyl)carbamate
10 hydrochloride (XXXV, PREPARATION 14, 300 mg, 0.43 mmole) and NMM (0.19 ml, 1.72 mmole). The reaction is stirred 3 hrs then concentrated under reduced pressure. The residue is partitioned between ethyl acetate and saturated aqueous bicarbonate. The organic phases are washed with aqueous
15 potassium bisulfate, saline, dried over sodium sulfate and finally concentrated under reduced pressure to give crude product. Purification via flash chromatography with ethyl acetate/hexane (50/50) then methanol/ethyl acetate (10/90) gives the title compound, M + H = 838 g/m.

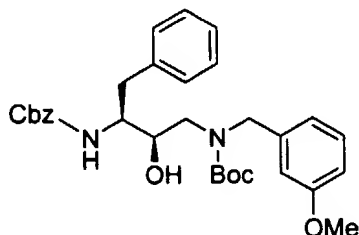
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PREPARATION 16 1- N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl)-5-oxo-5-(1-piperidiny]pentanamide trifluoroacetate X



1- N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl)-5-oxo-5-(1-piperidinyl)pentanamide trifluoroacetate (XXXVI, PREPARATION 15, 240 mg, 0.29 mmole is dissolved in diethylamine (10%, 9 ml) in methylene chloride. The reaction is stirred at 20-25° overnight. Next morning the reaction is concentrated under reduced pressure and the residue is redissolved in methylene chloride and purified by preparative reverse phase HPLC. The appropriate fractions are pooled and concentrated under reduced pressure and partitioned between ethyl acetate and saline. The organic phase is separated and dried over sodium sulfate and concentrated to give the title compound, M + H = 614.

15 PREPARATION 17 1-tert-butyl (2R,3S)-3-benzyloxycarbonylamino-2-hydroxy-4-phenylbutyl (3-methoxybenzyl) carbamate (XXXIV)



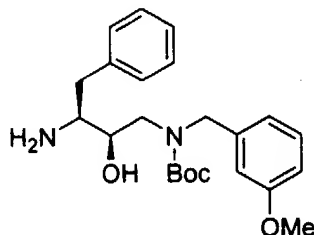
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1-benzyl (1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propylcarbamate hydrochloride (VII, PREPARATION 9, 8.16 g, 18.8 mmole) is mixed with THF (150 ml). The reaction mixture is cooled to 0° and treated with triethylamine (2.9 ml, 20.6 mmole) and di-t-butyl pyrocarbonate (4.1 g, 18.8 mmole). The reaction mixture is stirred at 20-25° for 3 hours. The reaction mixture is concentrated under reduced pressure and the residue is partitioned between ethyl acetate and aqueous citric acid (5 %). The organic phase is separated and washed with saturated aqueous bicarbonate,

30

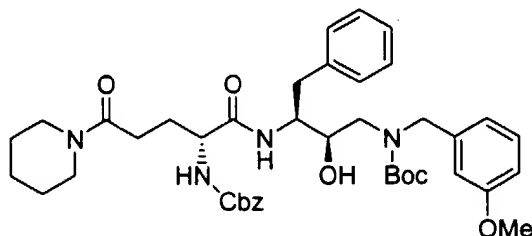
saline, dried over sodium sulfate and concentrated to give the title compound (96% purity by HPLC).

PREPARATION 18 1-tert-butyl (2R,3S)-3-amino-2-hydroxy-4-phenylbutyl(3-methoxybenzyl) carbamate (XXXV)



1-tert-butyl (2R,3S)-3-benzyloxycarbonylamino-2-hydroxy-4-phenylbutyl(3-methoxybenzyl) carbamate (XXXIV, EXAMPLE 1, 9.47 g), palladium-on-carbon (wet, 5%, 1.9 g) and methanol (95 ml) are added to a 300 ml Fisher Porter bottle. The reaction mixture is charged with hydrogen (50 psi) and hydrogenated for 1.2 hours until gas uptake ceased. The reaction mixture is filtered thru celite and concentrated under reduced pressure to give the title compound, M+H = 401.

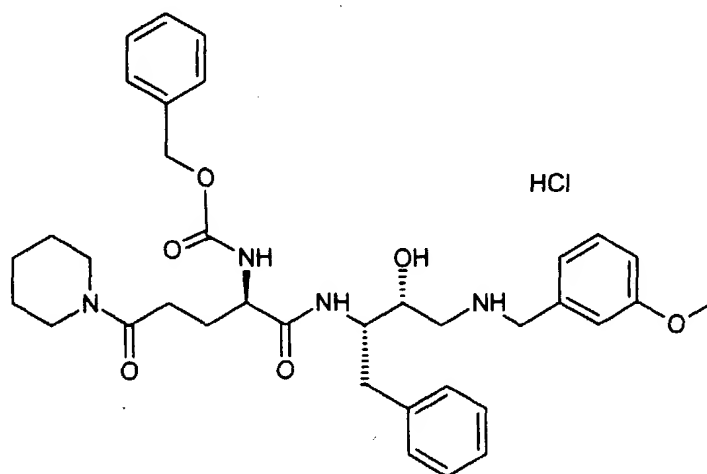
PREPARATION 19 1-Benzyl (1S)-1-[(1S,2R)-1-benzyl-3-[(tert-butoxycarbonyl)(3-methoxybenzyl)amino]-2-hydroxypropyl]amino)carbonyl]-4-oxo-4-(1-piperidinyl)butylcarbamate (XXXVI)



1- (2S)-2-[[(Benzyloxy) carbonyl] amino]-5-oxo-5-(1-piperidinyl)pentanoic (IX, 1.1 g), HOBt (0.64 g, 1.5 eq) and

EDC (700 mg, 1.15 eq) and DMF (4 ml) are mixed. The acid is activated for 20 minutes and then treated with 1-tert-butyl (2R,3S)-3-amino-2-hydroxy-4-phenylbutyl(3-methoxybenzyl) carbamate (XXXV, EXAMPLE 2, 1.3 g) and NMM (0.65 g, 2 eq) in DMF (4 ml). The reaction mixture is stirred 14 hours then concentrated under reduced pressure. The residue is partitioned between ethyl acetate and saturated aqueous bicarbonate. The organic phase is separated and washed with aqueous potassium bisulfate, saline, dried over sodium sulfate and concentrated under reduced pressure to give crude product. The crude product is purified via flash chromatography eluting with ethyl acetate (100 %) to give the title compound, M + H = 731.

15 PREPARATION 20 (2R)-2-Carbobenzyloxyamino-N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-5-oxo-5-piperidin-1-ylpentanamide hydrochloride X

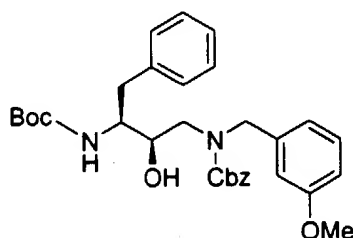


20 A 50 ml round bottom flask was charged with 1-benzyl (1S)-1-[[[(1S,2R)-1-benzyl-3-[(tert-butoxycarbonyl)(3-methoxybenzyl)amino]-2-hydroxypropyl]amino)carbonyl]-4-oxo-4-(1-piperidinyl)butylcarbamate (XXXVI, EXAMPLE 3, 100 mg) in dioxane/hydrochloric acid (4 N, 4 ml). The reaction is stirred 15 minutes when HPLC analysis indicates complete de-protection.

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The reaction mixture is concentrated under reduced pressure.
The crude product is chased with acetonitrile (5 ml) then
methylene chloride (5 ml). The resulting hydrochloride salt is
dried under reduced pressure, to give the title compound, M + H
5 = 631.

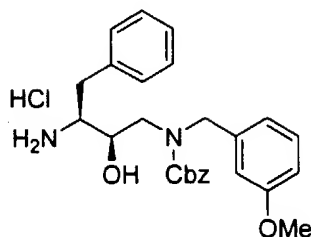
PREPARATION 21 1-tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propylcarbamate (XXXIV)



10

tert-Butyl (1S, 2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propylcarbamate (VII, PREPARATION 8, 19.2
g, 48 mmole) in THF (100 ml). The reaction mixture is cooled
15 to 0° and treated with N-benzyloxy carbonyloxysuccinamide (11.9
g, 48 mmole) while maintaining temperature < 5°. The reaction
mixture is stirred overnight and in the morning is concentrated
under reduced pressure. The residue is partitioned between
ethyl acetate and saturated aqueous bicarbonate. The organic
20 phase is separated and washed with citric acid (5%), saline,
dried over sodium sulfate and concentrated. The crude product
is purified by preparatory HPLC eluting with a gradient of from
20/80-50/50 ethyl acetate. To give the title compound, M + H =
534.

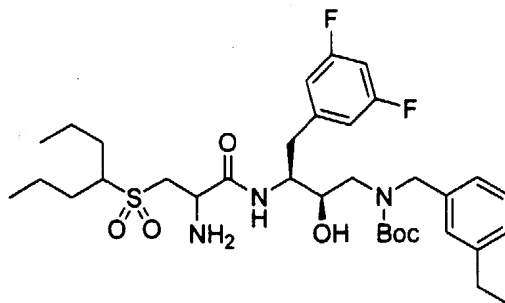
25
PREPARATION 22 (2R,3S)-3-amino-2-hydroxy-4-phenylbutyl(3-methoxybenzyl)carbamate hydrochloride. (XXXV)



1-tert-butyl (1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propylcarbamate (XXXIV, EXAMPLE 5, 5.4 g) and dioxane-hydrochloric acid (20 ml, 4 N) are mixed. The reaction mixture is stirred at 20-25° for 30 minutes then poured into stirred ether (300 ml). The product is filtered and dried under reduced pressure to give the title compound, M + H = 435.

10

PREPARATION 23 tert-butyl (2R,3S)-4-(3,5-difluorophenyl)-2-hydroxy-3-((3-[(1-propylbutyl)sulfonyl]alanyl)amino)butyl(3-ethylbenzyl)carbamate (LXXXVII)



15 Methyl 2-acetamidoacrylate (LXXX, 5.0 g, 34 mmole) and 4-mercaptoheptane (4.6 g, 34 mmole) in methanol (50 ml) are mixed. Triethylamine (3.6 g, 36 mmole) is added and the mixture is stirred at 20-25° for 45 minutes. The reaction vessel is then treated with oxone (47.2 g, 77 mmole). After 90
20 minutes HPLC indicated complete oxidation to the desired sulfone (LXXXII). The reaction mixture is filtered and concentrated under reduced pressure. The residue is partitioned between ethyl acetate and water and the organic

phase is separate and is washed with saline, dried over sodium sulfate, and concentrated under reduced pressure to give methyl N-acetyl-3-[(1-propylbutyl)sulfonyl]alaninate (LXXXII), $M + H = 308$ g/m.

5 Methyl N-acetyl-3-[(1-propylbutyl)sulfonyl]alaninate (LXXXII, 9.2 g) in acetic acid (50 ml) and concentrated hydrochloric acid (50 ml). The mixture is refluxed for 4 hours then concentrated under reduced pressure. The residue is chased with toluene (2 x) then vacuum dried overnight to give
10 3-[(1-propylbutyl)sulfonyl]alanine hydrochloride salt (LXXXIII).

3-[(1-Propylbutyl)sulfonyl]alanine (LXXXIII, 7.8 g, 27 mmole) and N-CBZ succinamide (7.4 g, 30 mmole) are mixed in methylene chloride (100 ml). The reaction is cooled to 0° , and
15 NMM (6.9 g) is added dropwise. The reaction is allowed to warm to $20-25^{\circ}$ and stirred for 4 hours at which point HPLC analysis indicated complete reaction. The reaction mixture is concentrated under reduced pressure and partitioned between ethyl acetate and hydrochloric acid (1 N). The organic phase
20 is washed with water, saline, dried over sodium sulfate, and concentrated under reduced pressure to give N-[(benzyloxy)carbonyl]-3-[(1-propylbutyl)sulfonyl]alanine (LXXXIV) that is used without further purification, $M + H = 386$.

25 N-[(benzyloxy)carbonyl]-3-[(1-propylbutyl)sulfonyl]alanine (LXXXIV, 4.0 g, 10 mmole) and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride (1.2 g, 12 mmole) are mixed in anhydrous methylene chloride (50 ml). To the reaction mixture is added
30 NMM (5.6 ml, 51 mmole), hydroxybenzotriazole (1.7 g, 13 mmole) and lastly 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (3.1 g (16 mmole)). After stirring at $20-25^{\circ}$ for 3 hours, HPLC analysis indicates complete reaction. The reaction mixture is diluted with methylene chloride and washed

with saturated sodium bicarbonate solution, citric acid (0.5 M), and saline. The organic phase is dried over sodium sulfate, filtered, and concentrated under reduced pressure to give N²-[(benzyloxy)carbonyl]-N¹-{(1S,2R)-1-(3,5-

5 difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]alaninamide (LXXXV).

N²-[(benzyloxy)carbonyl]-N¹-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]alaninamide (LXXXV) is dissolved in
10 anhydrous methylene chloride. The mixture is cooled to 0° and di-tert-butyl dicarbonate (2.5 g, 12 mmole) and N-methyl morpholine (1.2 ml, 11 mmole) are added. The reaction mixture is allowed to warm to 20-25° and stirred for 18 hours at which point HPLC analysis indicates complete reaction. The reaction
15 mixture is diluted with methylene chloride and washed with saturated sodium bicarbonate solution, and saline. The phases are separated and the organic phase is dried over sodium sulfate, filtered, and concentrated under reduced pressure. The concentrate is purified on silica gel by flash
20 chromatography using a gradient solvent of ethyl acetate/hexane (5/94 to 40/60) to give N²-[(benzyloxy-)carbonyl]-N¹-{(1S,2R)-N-[(t-butyloxy)carbonyl]-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide (LXXXVI), M + Na = 824.

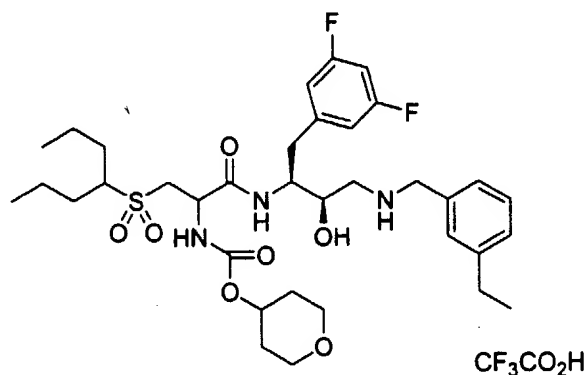
25 N²-[(benzyloxy-)carbonyl]-N¹-{(1S,2R)-N-[(t-butyloxy)carbonyl]-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide (LXXXVI, 3.4 g, 4.2 mmole) in methanol (50 ml) is added to a Fisher-Porter bottle.
30 After degassing with nitrogen, palladium on carbon (5% Pd/C, 1.6 g, Degussa E101 50% water) is added. The reaction vessel is purged with nitrogen (40 psi, 4 x) then pressurized to 50 psi with hydrogen. After 15 minutes, HPLC analysis indicates complete reaction. The catalyst is removed by filtration

through celite, and the filtrate concentrated under reduced pressure to give N¹-{(1S,2R)- N-[(t-butyloxy)carbonyl]-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alanine (LXXXVII), M+H = 668.

5

PREPARATION 24 N¹-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N²-{[tetrahydropyran-4-yloxy]carbonyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide trifluoroacetate (X-LXXXIX)

10



Tetrahydro-4H-pyran-4-ol (1.0 g, 9.8 mmole) is mixed with acetonitrile (50 ml). Di-(N-succinimidyl)carbonate (3.5 g, 13.5 mmole) is then added and stirred for 42 hours at 20-25°.

15 The reaction mixture is then concentrated under reduced
pressure, redissolved in ethyl acetate, and washed with aqueous
hydrochloric acid (1 N), saturated sodium bicarbonate solution,
and saline. The phases are separated and the organic phase is
dried over sodium sulfate, filtered, and concentrated under
20 reduced pressure. The crude material is recrystallized from
hot ethyl acetate and hexane to give 1-[[tetrahydro-2H-pyran-
4-yloxy)carbonyl]oxy}pyrrolidine-2,5-dione, $M + Na = 266$.

N¹-{(1S,2R)- N-[(benzyloxy)carbonyl]-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-
25 [(1-propylbutyl)sulfonyl]-D,L-alanine (LXXXVII, EXAMPLE 101,
251 mg, 0.31 mmole) is mixed with 1-[(tetrahydro-2H-pyran-4-
yloxy)carbonyl]-oxy}pyrrolidine-2,5-dione (100 mg) in methylene

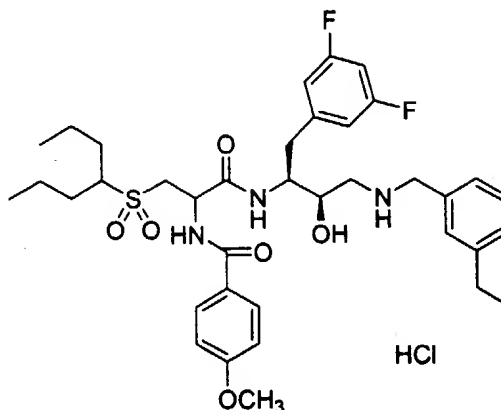
chloride (3 ml). Triethylamine (70 μ l, 0.51 mmole) is added and the mixture stirred at 20-25° overnight. The reaction mixture is diluted with ethyl acetate and washed with citric acid (5%), saturated sodium bicarbonate solution, and saline.

- 5 The phases are separated and the organic phase is dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude material is purified by reverse phase HPLC using a gradient solvent of acetonitrile in water with 0.5% trifluoroacetic acid to give of N¹-{(1S,2R)-N-
- 10 [(benzyloxy)carbonyl]-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N²-{[tetrahydropyran-4-yloxy]carbonyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide (LXXXVIII, M + H = 830.

- N¹-{(1S,2R)-N-[(benzyloxy)carbonyl]-1-(3,5-
- 15 difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N²-{[tetrahydropyran-4-yloxy]carbonyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide (LXXXVIII, 163 mg, 0.20 mmole) in methanol/tetrahydrofuran (1/1, 10 ml) is added to a Fisher-Porter bottle. After degassing with nitrogen, palladium
- 20 on carbon (5% Pd/C, 88 mg, Degussa E101 50% water) is added. The reaction vessel is purged with 40 psi nitrogen (4 x) then pressurized to 50 psi with hydrogen. After 25 minutes, HPLC analysis indicates the reaction is complete. The catalyst is removed by filtration through celite, and the filtrate
- 25 concentrated under reduced pressure. The crude material is purified by reverse phase HPLC using a gradient solvent of acetonitrile in water with 0.5% trifluoroacetic acid to give N¹-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-
- 30 hydroxypropyl}-N²-{[tetrahydropyran-4-yloxy]carbonyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide trifluoroacetate (X-LXXXIX), M+H = 696.

PREPARATION 25 N¹-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N²-(4-methoxybenzoyl)-3-

[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride (X-LXXXIX)

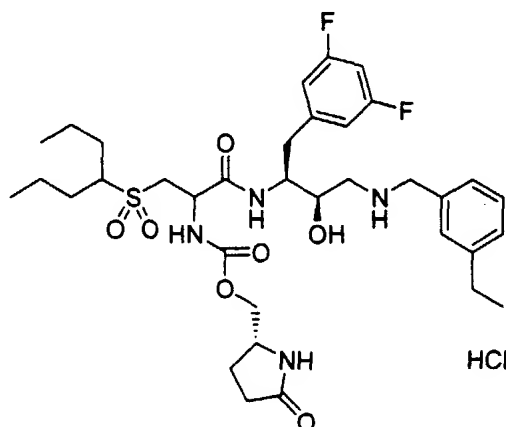


5 N¹-((1S,2R)- N-[(t-benzyloxy)carbonyl]-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alanine (LXXXVII, EXAMPLE 101, 150 mg, 0.22 mmole) in methylene chloride (1 ml). p-anisoyl chloride (32 μ l, 0.22 mmole) and 4-methylmorpholine (60 μ l, 10 0.55 mmole) are added. After stirring at 20-25° for 10 minutes, HPLC indicates the reaction is complete. The reaction mixture is diluted with ethyl acetate and washed with saturated sodium bicarbonate solution, citric acid (5%) and saline. The phases are separated and the organic phase is dried over sodium 15 sulfate, filtered, and concentrated under reduced pressure. The crude material is purified on silica gel using flash chromatography (ethyl acetate 20-50% in hexane as eluant to give N¹-((1S,2R)-N-[(t-butyloxy)carbonyl]-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)-amino]-2-hydroxypropyl)-N²-(4-methoxybenzoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide, 20 (LXXXVIII) M+H = 802.

N¹-((1S,2R)-N-[(t-butyloxy)carbonyl]-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)-amino]-2-hydroxypropyl)-N²-(4-methoxybenzoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide, 25 (LXXXVIII, 114 mg, 0.14 mmole) in hydrochloric acid (4 N, 1 ml) in dioxane. After stirring for 10 minutes at 20-25°, the

5

10



The compound of example 101(200 mg, 0.30 mmole) and 1-
25 [({((2S)-5-oxopyrrolidin-2-yl)methoxy}carbonyl)oxy]pyrrolidine-
2,5-dione (108 mg, 0.45 mmole) are mixed in methylene chloride

(5 ml). To the reaction mixture is added triethylamine (60 µl, 0.45 mmole) and stirred at 20-25° overnight. The reaction mixture is diluted with ethyl acetate and washed with citric acid (5%), saturated sodium bicarbonate solution, and saline.

5 The organic phase is dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude material was purified by reverse phase HPLC using a gradient solvent of acetonitrile in water with 0.5% trifluoroacetic acid to give N¹-{(1S,2R)-}

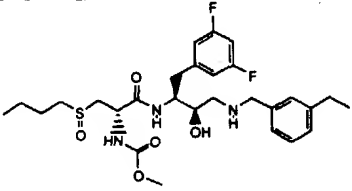
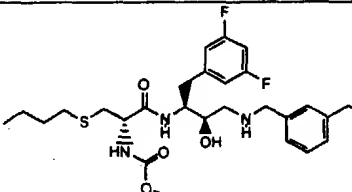
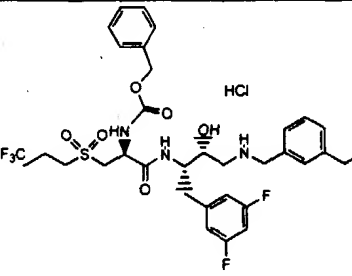
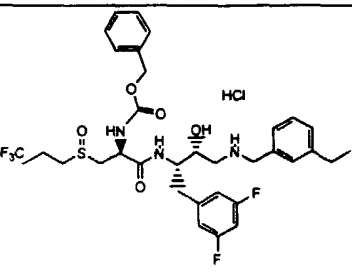
10 butyloxy)carbonyl))-1-(3,5-difluorobenzyl)-3-[(N-[(t-butylloxy)carbonyl]))-(3-ethylbenzyl)amino]-2-hydroxypropyl}-N²-{[[[(3R)-5-oxopyrrolidin-3-yl]methyl]oxy]carbonyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide, M+H = 809.

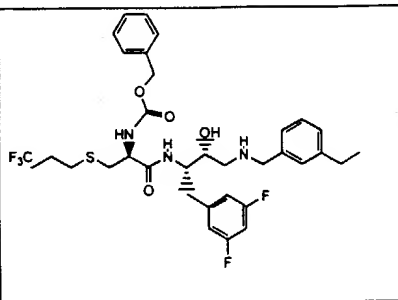
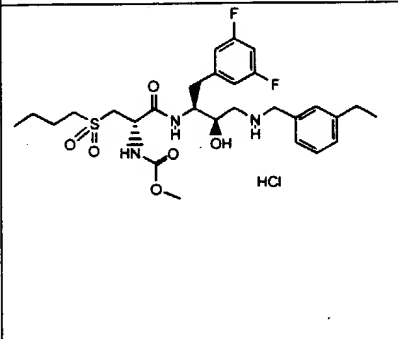
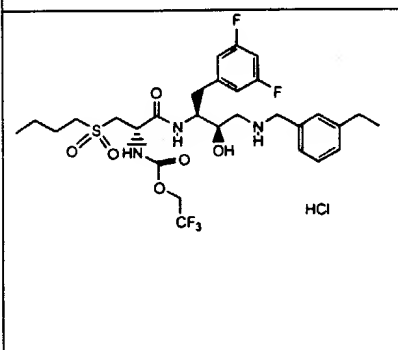
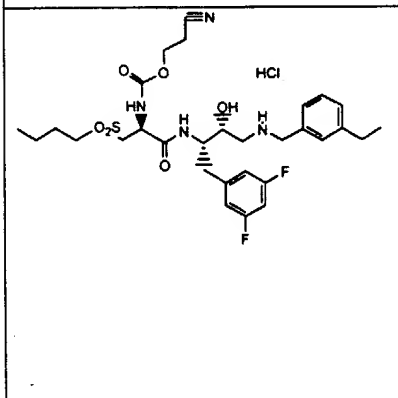
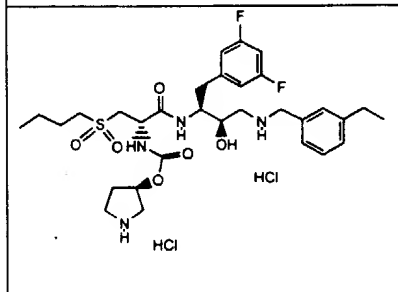
N¹-{(1S,2R)-} -1-(3,5-difluorobenzyl)-3-[(N-[(t-butylloxy)carbonyl]))-(3-ethylbenzyl)amino]-2-hydroxypropyl}-N²-
15 {[[[(3R)-5-oxopyrrolidin-3-yl]methyl]-oxy]carbonyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide (247 mg, 0.31 mmole) is mixed with dioxane (2 ml, 4 N hydrochloric acid). After stirring for 10 minutes at 20-25°, the solvent was removed under reduced pressure to give the title compound, M+H = 709.

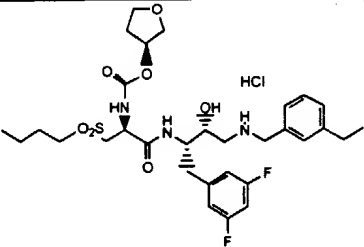
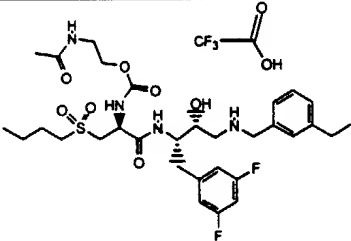
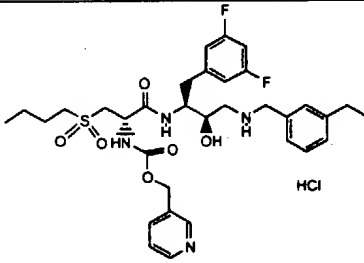
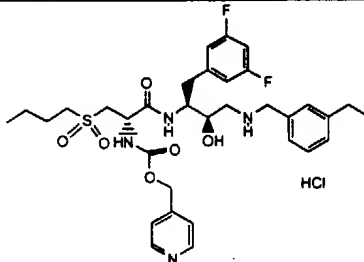
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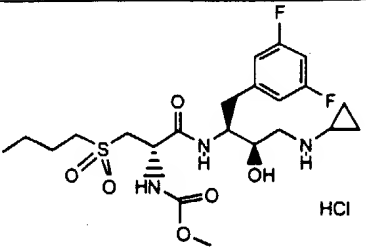
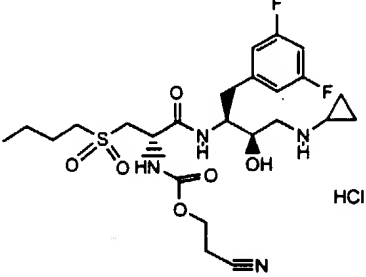
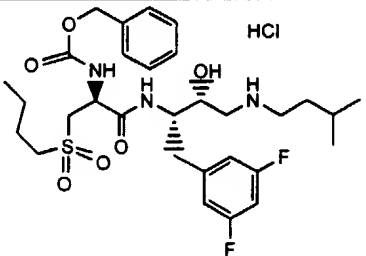
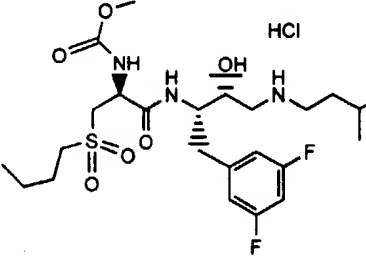
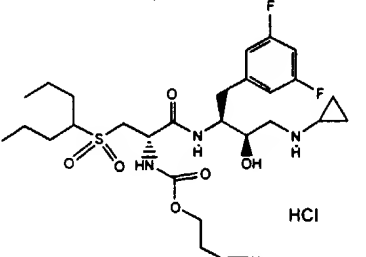
The following compounds in table 1 are prepared essentially according to the procedures described in the schemes, examples and preparations set forth herein. The names in table 1 were generated at least in part by using the
25 Advanced Chemistry Development Inc. (ACD) nomenclature program, IUPAC Name Batch Version 4, 4.5 or 5, or Chemdraw Ultra versions 6.0 or 6.02.

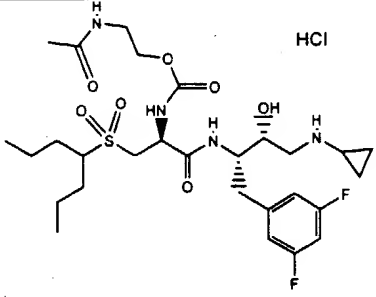
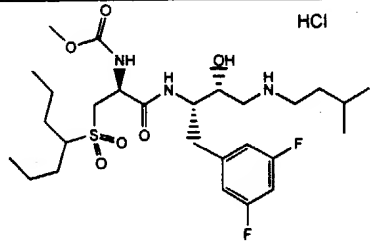
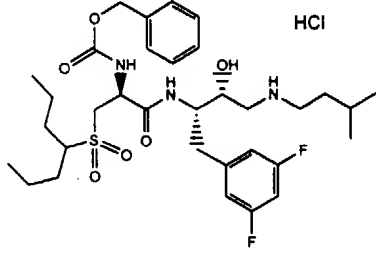
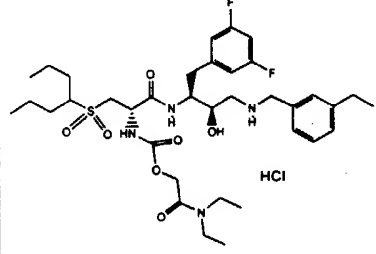
Table 1

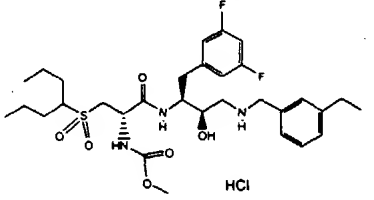
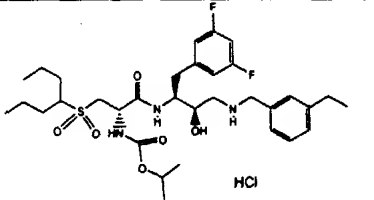
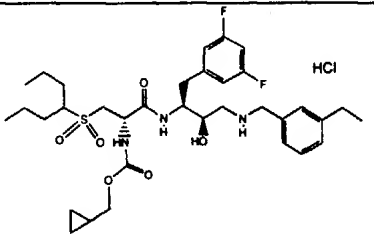
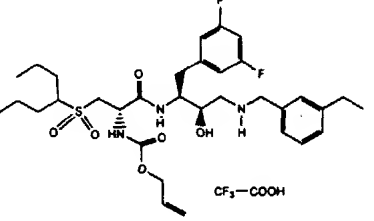
Structure	Compound Name(s)	Low Res Mass Spec M+H
	3-(butylsulfinyl)-N-1-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-N-2-((methoxy)carbonyl)-D-alaninamide	568
	S-butyl-N-1-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-N-2-((methoxy)carbonyl)-D-cysteinamide	552
	N-2-((benzyloxy)carbonyl)-N-1-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-3-((4,4,4-trifluorobutyl)sulfonyl)-D-alaninamide hydrochloride	714
	N-2-((benzyloxy)carbonyl)-N-1-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-3-((4,4,4-trifluorobutyl)sulfinyl)-D-alaninamide hydrochloride	698

	N-2--[(benzyloxy)carbonyl]- N-1--{(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-S-(4,4,4- trifluorobutyl)-D-cysteinamide	682
	3-(butylsulfonyl)-N-1-- {(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-N-2-- [(methoxy)carbonyl]-D- alaninamide hydrochloride	584
	3-(butylsulfonyl)-N-1-- {(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-N-2--[(2,2,2- trifluoroethoxy)carbonyl]-D- alaninamide hydrochloride	652
	N-2--[(2- cyanoethoxy)carbonyl]-N-1-- {(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-3- (butylsulfonyl)-D-alaninamide hydrochloride	623
	3-(butylsulfonyl)-N-1-- {(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-N-2--[(3R)- pyrrolidin-3-yl]carbonyl}-D,L-	639

	alaninamide dihydrochloride	
	3-(butylsulfonyl)-N-1-- {(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-N-2--{[(3S)- tetrahydrofuran-3- yloxy]carbonyl}-D-alaninamide hydrochloride	640
	N-2--{[2- (acetylamino)ethoxy]carbonyl}- 3-(butylsulfonyl)-N-1-- {(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-D-alaninamide trifluoroacetate	655
	3-(butylsulfonyl)-N-1-- {(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-N-2-- {[(pyridin-3- yl)methyl]oxy]carbonyl}-D- alaninamide hydrochloride	661
	3-(butylsulfonyl)-N-1-- {(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-N-2-- {[(pyridin-4- yl)methyl]oxy]carbonyl}-D- alaninamide hydrochloride	661

	<p>3-(butylsulfonyl)-N2- [(methoxy)carbonyl]-N1-- {(1S,2R)-1-(3,5- difluorobenzyl)-3- (cyclopropylamino)-2- hydroxypropyl}-D-alaninamide hydrochloride</p>	506
	<p>3-(butylsulfonyl)-N2-[(2- cyanoethoxy)carbonyl]-N1-- {(1S,2R)-1-(3,5- difluorobenzyl)-3- (cyclopropylamino)-2- hydroxypropyl}-D-alaninamide hydrochloride</p>	545
	<p>N2-[(benzyloxy)carbonyl]-3- (butylsulfonyl)-N1--{(1S,2R)- 1-(3,5-difluorobenzyl)-3-[(3- methylbutyl)amino]-2- hydroxypropyl}-D-alaninamide hydrochloride</p>	612
	<p>3-(butylsulfonyl)-N1-- {(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- methylbutyl)amino]-2- hydroxypropyl}-N2- [(methoxy)carbonyl]-D- alaninamide hydrochloride</p>	536
	<p>N2-[(2- cyanoethoxy)carbonyl]-N1-- {(1S,2R)-1-(3,5- difluorobenzyl)-3- (cyclopropylamino)-2- hydroxypropyl}-3-[(1- propylbutyl)sulfonyl]-D-</p>	587

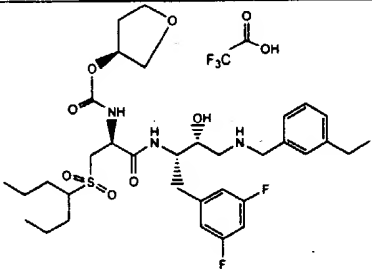
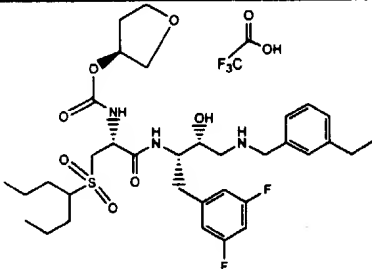
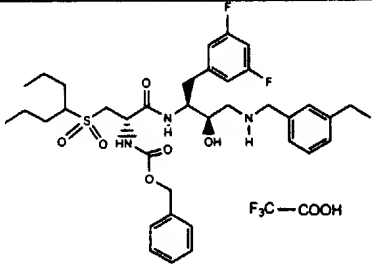
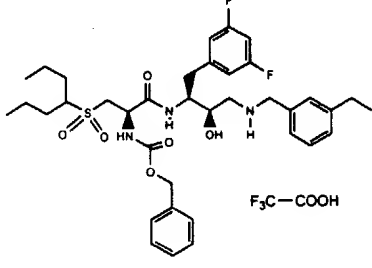
	alaninamide hydrochloride	
	<p>N-2--{[2-(acetylamino)ethoxy]carbonyl}-</p> <p>N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-((cyclopropylamino)-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide hydrochloride</p>	619
	<p>N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-methylbutyl)amino]-2-hydroxypropyl}-N-2--[(methoxy)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D-alaninamide hydrochloride</p>	578
	<p>N-2--[(benzyloxy)carbonyl]-</p> <p>N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-methylbutyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide hydrochloride</p>	654
	<p>N-2--{[2-(diethylamino)-2-oxoethoxy]carbonyl}-N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide hydrochloride</p>	725

	<p>N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N-2--[(methoxy)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D-alaninamide hydrochloride</p>	626
	<p>N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N-2--[(isopropoxy)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D-alaninamide hydrochloride</p>	654
	<p>N-2--[(cyclopropylmethoxy)carbonyl]-N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide hydrochloride</p>	666
	<p>N-2--[(allyloxy)carbonyl]-N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide trifluoroacetate</p>	652

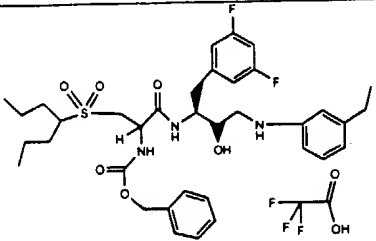
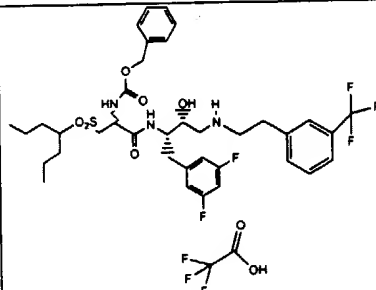
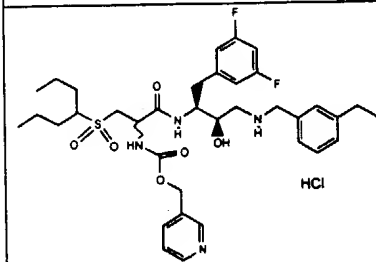
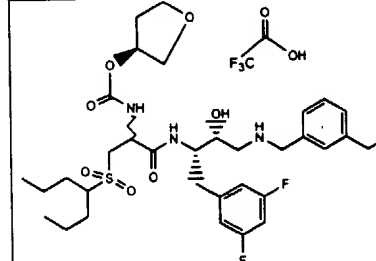
	<p>N-2--[(2-cyanoethoxy)carbonyl]-N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide trifluoroacetate</p>	665
	<p>N-2--{[2-(acetylamino)ethoxy]carbonyl}-N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide hydrochloride</p>	697
	<p>N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-N-2--{[[(pyridin-3-yl)methyl]oxy]carbonyl}-D-alaninamide hydrochloride</p>	703
	<p>N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-N-2--{[[(pyridin-4-yl)methyl]oxy]carbonyl}-D-alaninamide hydrochloride</p>	703

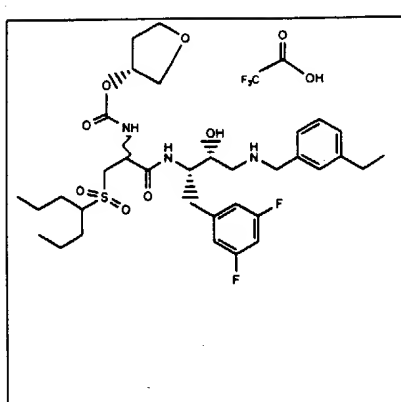
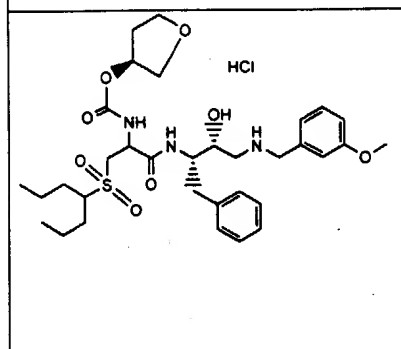
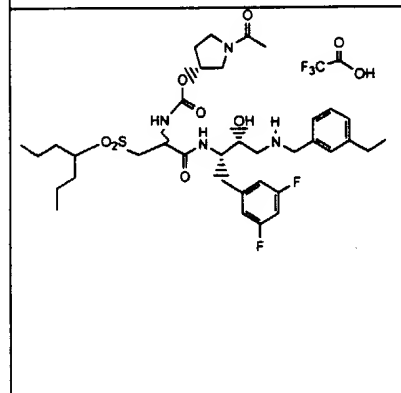
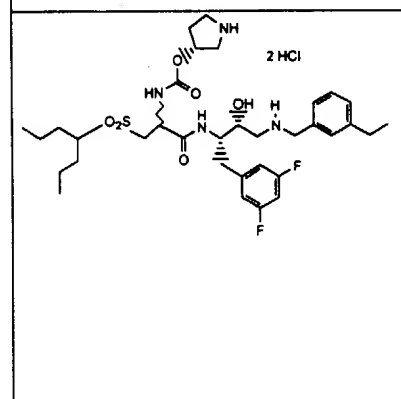
	benzyl (1R)-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]amino carbonyl-(methanesulfonyl)propylcarbamate	632
	N-2-[(benzyloxy) carbonyl]-3-(butylsulfonyl)-N-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-D-alaninamide trifluoroacetate	660
	N-2-[(benzyloxy) carbonyl]-3-(butylsulfonyl)-N-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-L-alaninamide trifluoroacetate	660
	N-2-[(benzyloxy) carbonyl]-N-1-[(1S,2S)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1R)-2-hydroxy-1-phenylethyl]amino]propyl-3-[(1-propylbutyl)sulfonyl]-D-alaninamide	704
	N-2-[(benzyloxy) carbonyl]-N-1-[(1S,2S)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1R)-2-methoxy-1-phenylethyl]amino]propyl-3-[(1-propylbutyl)sulfonyl]-D-alaninamide	718

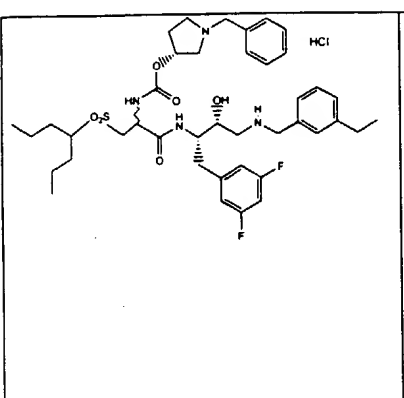
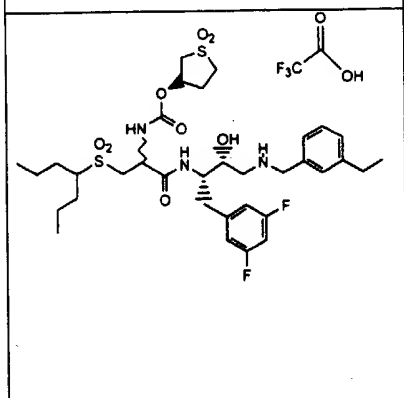
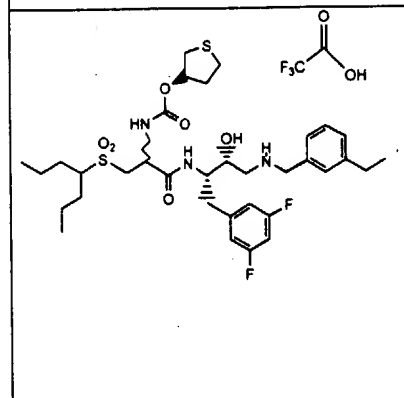
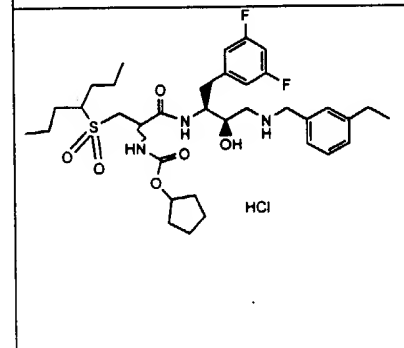
	<p>N-2-~[(benzyloxy)carbonyl]- N-1-~((1S,2S)-1-(3,5- difluorobenzyl)-2-hydroxy-3- {[(1S)-2-methoxy-1- phenylethyl]amino}propyl)-3- [(1-propylbutyl)sulfonyl]-D- alaninamide</p>	718
	<p>N-2-~[(benzyloxy)carbonyl]- N-1-~((1S,2R)-1-(3,5- difluorobenzyl)-3-{[1-(3- ethylphenyl)cyclopropyl]amino} -2-hydroxypropyl)-3-[(1- propylbutyl)sulfonyl]-D- alaninamide</p>	728
	<p>N-1-~((1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl)-3-[(1- propylbutyl)sulfonyl]-N-2-~ {[(prop-2-ynyl)oxy]carbonyl}- D-alaninamide trifluoroacetate</p>	650
	<p>N-1-~((1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl)-N-2-~(2- methoxyethylcarbonyl)-3-[(1- propylbutyl)sulfonyl]-D- alaninamide hydrochloride</p>	670
	<p>N-2-~{[(3R)-1- acetylpyrrolidin-3- yl]carbonyl}-N-1-~((1S,2R)-1- (3,5-difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl)-3-[(1-</p>	723

	propylbutyl)sulfonyl]-D-alaninamide hydrochloride	
	N-1-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-N-2-((3S)-tetrahydrofuran-3-yloxy)carbonyl)-3-((1-propylbutyl)sulfonyl)-D-alaninamide trifluoroacetate	682
	N-1-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-N-2-((3S)-tetrahydrofuran-3-yloxy)carbonyl)-3-((1-propylbutyl)sulfonyl)-L-alaninamide trifluoroacetate	682
	N-2-((benzyloxy)carbonyl)-N-1-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-3-((1-propylbutyl)sulfonyl)-D-alaninamide trifluoroacetate	702
	N-2-((benzyloxy)carbonyl)-N-1-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-3-((1-propylbutyl)sulfonyl)-L-alaninamide trifluoroacetate	702

	<p>N-2--[(benzyloxy)carbonyl]- N-1--((1S,2R)-1-(3,5- difluorobenzyl)-3-{{[1-(3- ethylphenyl)cyclopropyl]amino} -2-hydroxypropyl}-3-[(1- propylbutyl)sulfonyl]-D,L- alaninamide trifluoroacetate</p>	728
	<p>N-2--[(benzyloxy)carbonyl]- N-1--((1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-3-[(1- propylbutyl)sulfonyl]-D,L- alaninamide trifluoroacetate</p>	702
	<p>N-2--[(benzyloxy)carbonyl]- N-1--((1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- methylbutyl)amino]-2- hydroxypropyl}-3-[(1- propylbutyl)sulfonyl]-D,L- alaninamide</p>	654
	<p>N-2--[(benzyloxy)carbonyl]- N-1--((1S,2R)-1-(3,5- difluorobenzyl)-3- (cyclopropylamino)-2- hydroxypropyl}-3-[(1- propylbutyl)sulfonyl]-D,L- alaninamide trifluoroacetate</p>	624
	<p>N-2--[(benzyloxy)carbonyl]- N-1--((1S,2R)-1-(3,5- difluorobenzyl)-3- [(cyclopropylmethyl)amino]-2- hydroxypropyl}-3-[(1- propylbutyl)sulfonyl]-D,L- alaninamide trifluoroacetate</p>	638

	propylbutyl) sulfonyl]-D,L- alaninamide trifluoroacetate	
	N-2--[(benzyloxy) carbonyl]- N-1--{(1S,2S)-1-(3,5- difluorobenzyl)-3-[(3- ethylphenyl) amino]-2- hydroxypropyl}-3-[(1- propylbutyl) sulfonyl]-D,L- alaninamide trifluoroacetate	688
	N-2--[(benzyloxy) carbonyl]- N-1--[(1S,2R)-1-(3,5- difluorobenzyl)-2-hydroxy-3- ({2-[3- (trifluoromethyl)phenyl]ethyl} amino)propyl]-3-[(1- propylbutyl) sulfonyl]-D,L- alaninamide trifluoroacetate	756
	N-1--{(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl) amino]-2- hydroxypropyl}-3-[(1- propylbutyl) sulfonyl]-N-2-- {[(pyridin-3- yl)methyl]oxy} carbonyl]-D,L- alaninamide hydrochloride	703
	N-1--{(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl) amino]-2- hydroxypropyl}-N-2--{[(3S)- tetrahydrofuran-3- yloxy] carbonyl}-3-[(1- propylbutyl) sulfonyl]-D,L- alaninamide trifluoroacetate	682

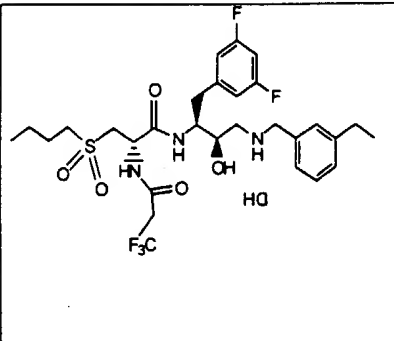
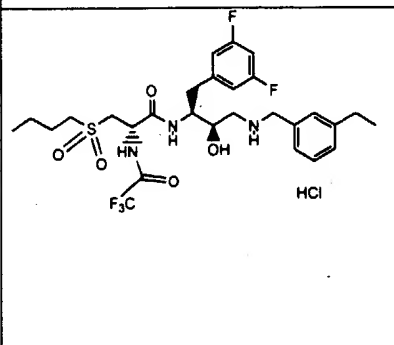
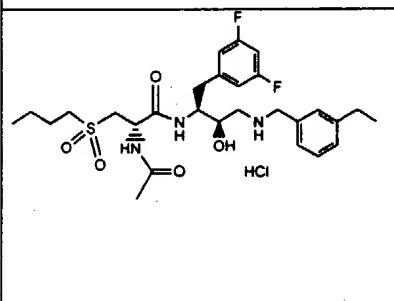
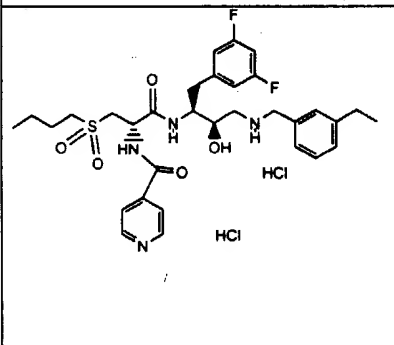
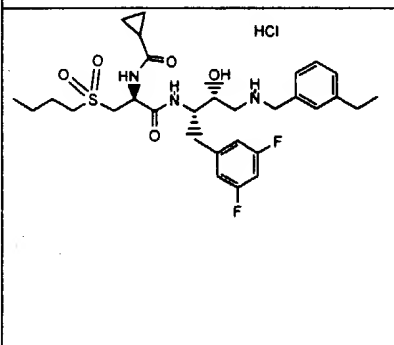
	<p>N-1-((1S,2R)-1-((3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-N-2-((3R)-tetrahydrofuran-3-yloxy)carbonyl)-3-((1-propylbutyl)sulfonyl)-D,L-alaninamide trifluoroacetate</p>	682
	<p>N-1-((1S,2R)-1-benzyl-3-((3-methoxybenzyl)amino)-2-hydroxypropyl)-N-2-((3S)-tetrahydrofuran-3-yloxy)carbonyl)-3-((1-propylbutyl)sulfonyl)-D,L-alaninamide hydrochloride</p>	648
	<p>N-2-((3R)-1-acetylpyrrolidin-3-yl)carbonyl)-N-1-((1S,2R)-1-((3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-3-((1-propylbutyl)sulfonyl)-D,L-alaninamide trifluoroacetate</p>	723
	<p>N-1-((1S,2R)-1-((3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-3-((1-propylbutyl)sulfonyl)-N-2-((3R)-pyrrolidin-3-yl)carbonyl)-D,L-alaninamide dihydrochloride</p>	681

	<p>N-2--{[(3R)-1-benzylpyrrolidin-3-yl]carbonyl}-N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride</p>	771
	<p>N-1--{(1S,2R)-1-(3,5difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N-2--{[(3S)-1,1-dioxidotetrahydrothien-3-yloxy]carbonyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide trifluoroacetate</p>	730
	<p>N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N-2--{[(3S)-tetrahydrothiophen-3-yloxy]carbonyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide trifluoroacetate</p>	698
	<p>N-2--(cyclopentylcarbonyl)-N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride</p>	680

	<p>N-2--(cyclohexylcarbonyl)- N-1--{(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-3-[(1- propylbutyl)sulfonyl]-D,L- alaninamide hydrochloride</p>	694
	<p>N-1--[(1S,2R)-3- (cyclopropylamino)-1-(3,5- difluorobenzyl)-2- hydroxypropyl]-3-[(1- propylbutyl)sulfonyl]-N-2-- {[tetrahydropyran-4- yloxy]carbonyl}-D,L- alaninamide hydrochloride</p>	618
	<p>N-1--{(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-3-[(1- propylbutyl)sulfonyl]-N-2-- {[tetrahydropyran-4- yloxy]carbonyl}-D,L- alaninamide trifluoroacetate</p>	696
	<p>N-1--{(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-N-2--{[1- (methylsulfonyl)piperidin-4- yloxy]carbonyl}-3-[(1- propylbutyl)sulfonyl]-D,L- alaninamide trifluoroacetate</p>	773

	N-2--{[1-acetylpiperidin-4-yloxy]carbonyl}-N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide trifluoroacetate	737
	N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N-2--{[[[(3S)-5-oxopyrrolidin-3-yl]methyl]oxy]carbonyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride	709
	N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N-2--{[[[(3R)-5-oxopyrrolidin-3-yl]methyl]oxy]carbonyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide trifluoroacetate	709
	N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N-2--{[2-methoxyethyl]oxy]carbonyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride	670

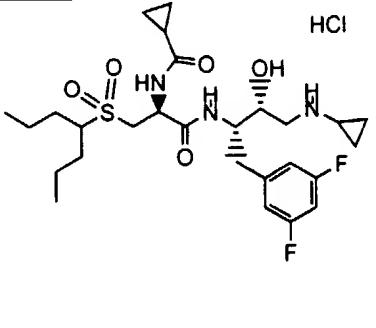
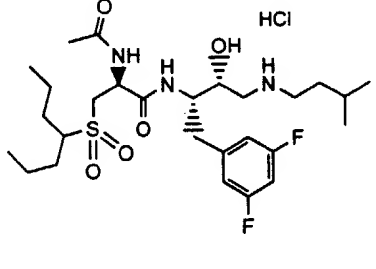
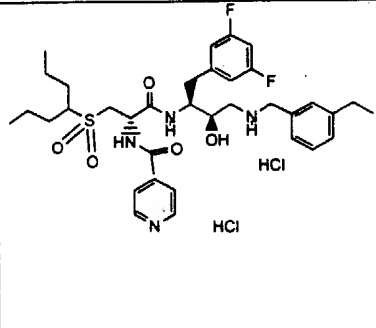
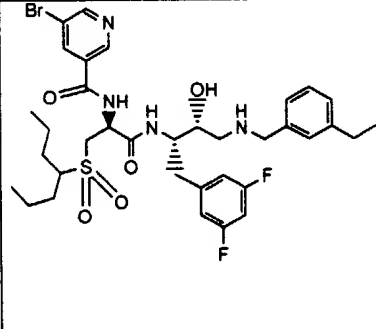
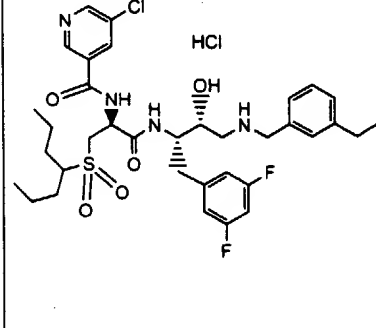
	N-2-[(benzyloxy)carbonyl]-3-(butylsulfonyl)-N-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-D,L-alaninamide	660
	N-1-[(1S,2R)-1-benzyl-3-[(3-methoxybenzyl)amino]-2-hydroxypropyl]-N-2-[(benzyloxy)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride	668
	N-2-[(benzyloxy)carbonyl]-N-1-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[2-(3-methoxyphenyl)ethyl]amino]propyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide trifluoroacetate	718
	N-2-[(benzyloxy)carbonyl]-N-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-N-5,N-5-dipropyl-L-glutamamide trifluoroacetate	681
	N-2-[(benzyloxy)carbonyl]-N-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-N-5,N-5-dipropyl-D-glutamamide	681

	3-(butylsulfonyl)-N-1-- {(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-N-2--(3,3,3- trifluoropropanoyl)-D- alaninamide hydrochloride	636
	3-(butylsulfonyl)-N-1-- {(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-N-2-- (trifluoroacetyl)-D- alaninamide hydrochloride	622
	N-2--acetyl-3-(butylsulfonyl)- N-1--{(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-D-alaninamide hydrochloride	568
	3-(butylsulfonyl)-N-1-- {(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-N-2--(pyridin- 4-ylcarbonyl)-D-alaninamide dihydrochloride	631
	3-(butylsulfonyl)-N-2-- (cyclopropylcarbonyl)-N-1-- {(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-D-alaninamide hydrochloride	594

	3-(butylsulfonyl)-N-1-- {(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-N-2~(beta- alanyl)-D-alaninamide dihydrochloride	597
	3-(butylsulfonyl)-N-1-- {(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-N-2~glycyl-D- alaninamide dihydrochloride	583
	3-(butylsulfonyl)-N-1-- {(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-N-2~(N,N- dimethylglycyl)-D-alaninamide dihydrochloride	611
	3-(butylsulfonyl)-N-1-- {(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-N-2~(N,N- dimethyl-beta-alanyl)-D- alaninamide dihydrochloride	625
	3-(butylsulfonyl)-N-1-- {(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-N-2-- (methoxyacetyl)-D-alaninamide	598

	<p>3-(butylsulfonyl)-N-1-- {(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-N-2--(pyridin- 3-ylcarbonyl)-D-alaninamide dihydrochloride</p>	631
	<p>3-(butylsulfonyl)-N-1-- {(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-N-2--[(2,4- dimethyl-1,3-thiazol-5- yl)carbonyl]-D-alaninamide hydrochloride</p>	665
	<p>3-(butylsulfonyl)-N-1-- {(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-N-2--[(3- (trifluoromethyl)-1H-pyrazol- 4-yl)carbonyl]-D-alaninamide hydrochloride</p>	688
	<p>3-(butylsulfonyl)-N-1-- {(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-N-2--[(3- methyl-1H-pyrazol-5- yl)carbonyl]-D-alaninamide hydrochloride</p>	634

	<p>3-(butylsulfonyl)-N-1-- {(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-N-2--(1H- imidazol-4-ylacetyl)-D- alaninamide dihydrochloride</p>	620
	<p>3-(butylsulfonyl)-N-1-- {(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-N-2--(pyrazin- 2-ylcarbonyl)-D-alaninamide dihydrochloride</p>	632
	<p>3-(butylsulfonyl)-N-1-- {(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-N-2--[(6- hydroxypyridin-3-yl)carbonyl]- D-alaninamide dihydrochloride</p>	647
	<p>N-1--{(1S,2R)-1-(3,5- difluorobenzyl)-3- (cyclopropylamino)-2- hydroxypropyl}-3-[(1- propylbutyl)sulfonyl]-N-2-- (pyridin-4-ylcarbonyl)-D- alaninamide dihydrochloride</p>	553
	<p>N-2--acetyl-3-(butylsulfonyl)- N-1--{(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- methylbutyl)amino]-2- hydroxypropyl}-D-alaninamide hydrochloride</p>	520

	<p>N-1-[(1S,2R)-3-((cyclopropylamino)-1-(3,5-difluorobenzyl))-2-hydroxypropyl]-N-2-[(cyclopropylcarbonyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide hydrochloride</p>	558
	<p>N-2-acetyl-N-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-methylbutyl)amino]-2-hydroxypropyl]-3-[(1-propylbutyl)sulfonyl]-D-alaninamide hydrochloride</p>	562
	<p>N-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-3-[(1-propylbutyl)sulfonyl]-N-2-[(pyridin-4-ylcarbonyl)-D-alaninamide dihydrochloride</p>	673
	<p>N-2-[(5-bromoopyridin-3-yl)carbonyl]-N-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-3-[(1-propylbutyl)sulfonyl]-D-alaninamide</p>	751
	<p>N-2-[(5-chloropyridin-3-yl)carbonyl]-N-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-3-[(1-propylbutyl)sulfonyl]-D-alaninamide hydrochloride</p>	707

	N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N-2-(3-fluorobenzoyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide hydrochloride	690
	N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N-2--[(5-methylpyridin-3-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D-alaninamide dihydrochloride	687
	N-2--phenylglycyl-N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide	701
	N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-N-2--{[3-(trifluoromethyl)-1H-pyrazol-4-yl]carbonyl}-D-alaninamide hydrochloride	730

	N-1--((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N-2--[(3-methyl-1H-pyrazol-5-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D-alaninamide hydrochloride	676
	N-1--((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]-N-2--(1,3-thiazol-4-ylcarbonyl)-D-alaninamide hydrochloride	679
	N-2--[(1-acetypiperidin-4-yl)carbonyl]-N-1--((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide hydrochloride	721
	N-2--[4-(acetylamino)butanoyl]-N-1--((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide hydrochloride	695

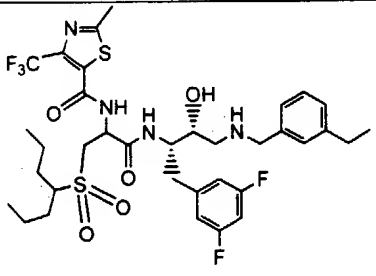
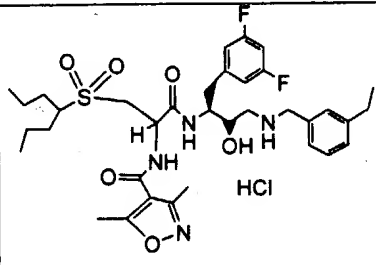
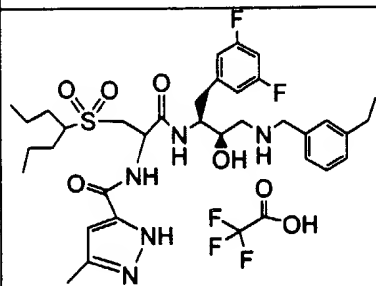
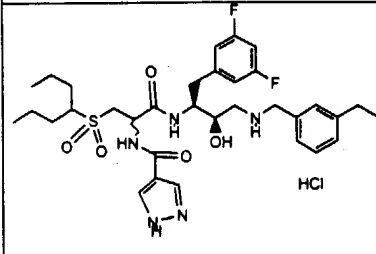
	<p>N-2--acetyl-beta-alanyl-N-1-- { (1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-3-[(1- propylbutyl)sulfonyl]-D- alaninamide hydrochloride</p>	681
	<p>N-2--(chloroacetyl)-N-1-- { (1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-3-[(1- propylbutyl)sulfonyl]-D- alaninamide hydrochloride</p>	644
	<p>N-1--{(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-N-2-- (methoxyacetyl)-3-[(1- propylbutyl)sulfonyl]-D- alaninamide</p>	640
	<p>N-1--{(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-N-2--(3- methoxypropanoyl)-3-[(1- propylbutyl)sulfonyl]-D- alaninamide</p>	654
	<p>N-1--{(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-N-2--(2,2- dimethylpropanoyl)-3-[(1- propylbutyl)sulfonyl]-D-</p>	652

	alaninamide hydrochloride	
	N-1-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-N-2-isobutyryl-3-((1-propylbutyl)sulfonyl)-D-alaninamide hydrochloride	638
	N-2-butyl-N-1-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-3-((1-propylbutyl)sulfonyl)-D-alaninamide hydrochloride	638
	N-2-acetyl-N-1-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-3-((1-propylbutyl)sulfonyl)-D-alaninamide hydrochloride	610
	N-1-((1S,2R)-1-(3,5-difluorobenzyl)-3-([1-(3-ethylphenyl)cyclopropyl]amino)-2-hydroxypropyl)-3-((1-propylbutyl)sulfonyl)-N-2-((pyridin-3-yl)carbonyl)-D-alaninamide trifluoroacetate	699
	N-1-((1S,2R)-1-(3,5-difluorobenzyl)-3-([1-(3-ethylphenyl)cyclopropyl]amino)-2-hydroxypropyl)-3-((1-propylbutyl)sulfonyl)-N-2-((pyridin-4-yl)carbonyl)-D-alaninamide trifluoroacetate	699

	N-1-((1S,2R)-1-(3,5-difluorobenzyl)-3-({[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-N-2-((3-hydroxybenzoyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide trifluoroacetate	714
	N-1-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]-N-2-((pyridin-3-yl)carbonyl)-D-alaninamide	673
	N-1-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N-2-((3-hydroxybenzoyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide	688
	N-2-((cyclopropylcarbonyl)-N-1-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide hydrochloride	636
	N-1-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N-2-propionyl-3-[(1-propylbutyl)sulfonyl]-D-alaninamide	624

	<p>3-[butylsulfonyl]-N-1-- {(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl)-N-2--[(pyridin- 3-yl)carbonyl]-D,L-alaninamide hydrochloride</p>	631
	<p>N-1--((1S,2R)-1-(3,5- difluorobenzyl)-3-[[1-(3- ethylphenyl)cyclopropyl]amino} -2-hydroxypropyl)-N-2--(3- hydroxybenzoyl)-3-[(1- propylbutyl)sulfonyl]-D,L- alaninamide trifluoroacetate</p>	714
	<p>N-1--((1S,2R)-1-(3,5- difluorobenzyl)-3-[[1-(3- ethylphenyl)cyclopropyl]amino} -2-hydroxypropyl)-3-[(1- propylbutyl)sulfonyl]-N-2-- [(pyridin-4-yl)carbonyl]-D- alaninamide trifluoroacetate</p>	699
	<p>N-1--((1S,2S)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl)-N-2--[(6-oxo- 1,4,5,6-tetrahydropyridazin-3- yl)carbonyl]-3-[(1- propylbutyl)sulfonyl]alaninami de hydrochloride</p>	692

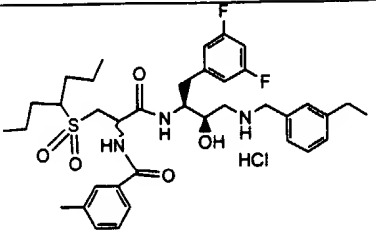
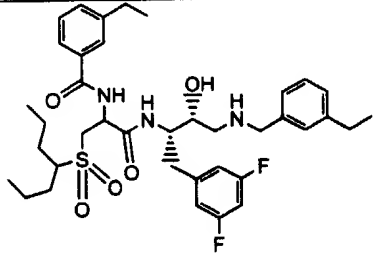
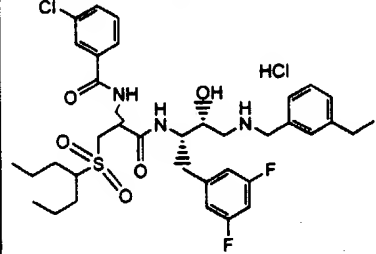
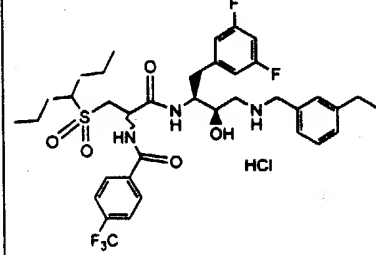
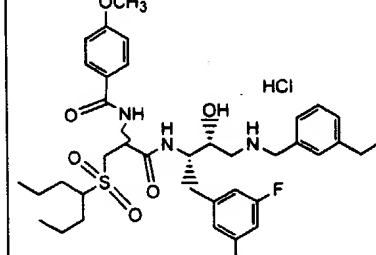
	5-oxo-D-prolyl-N-1-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-3-((1-propylbutyl)sulfonyl)alaninamide hydrochloride	679
	5-oxo-L-prolyl-N-1-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-3-((1-propylbutyl)sulfonyl)alaninamide hydrochloride	679
	N-1-((1S,2S)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-N-2-((3-(4-oxo-2-thioxo-1,3-thiazolidin-3-yl)propanoyl)-3-((1-propylbutyl)sulfonyl)alaninamide	755
	N-1-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-N-2-((piperidin-4-yl)carbonyl)-3-((1-propylbutyl)sulfonyl)-D,L-alaninamide dihydrochloride	679
	N-1-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-N-2-((2,4-dimethyl-1,3-thiazol-5-yl)carbonyl)-3-((1-propylbutyl)sulfonyl)-D,L-alaninamide hydrochloride	707

	alaninamide hydrochloride	
	N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(2-methyl-4-(trifluoromethyl)-1,3-thiazol-5-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide	761
	N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(3,5-dimethylisoxazol-4-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride	691
	N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(3-methyl-1H-pyrazol-5-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide trifluoroacetate	676
	N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(1H-pyrazol-4-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride	662

	<p>N-1--((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N-2--[(1H-imidazol-5-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride</p>	662
	<p>N-1--((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N-2--(1H-imidazol-4-ylacetyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide dihydrochloride</p>	676
	<p>N-1--((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]-N-2--[(pyrazin-2-yl)carbonyl]-D,L-alaninamide</p>	674
	<p>N-1--((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N-2--[(3,5-dihydroxypyridin-4-yl)carbonyl]--3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride</p>	705

	<p>N-1--((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N-2--[(6-hydroxypyridin-3-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide trifluoroacetate</p>	689
	<p>N-2--[(6-chloropyridin-3-yl)carbonyl]-N-1--((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride</p>	707
	<p>N-1--((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]-N-2--[(pyridin-4-yl)carbonyl]-D,L-alaninamide dihydrochloride</p>	673
	<p>N-1--((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N-2--[(pyridin-3-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide</p>	673
	<p>N-1--((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N-2--[(pyridin-3-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide</p>	673

	[(pyridin-2-yl)carbonyl]-D,L-alaninamide hydrochloride	
	N-1-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-N-2-((1H-indole-6-carbonyl)-3-((1-propylbutyl)sulfonyl))-D,L-alaninamide hydrochloride	711
	N-1-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-3-((1-propylbutyl)sulfonyl)-N-2-((2,3,4-trimethoxybenzoyl))-D,L-alaninamide hydrochloride	762
	N-1-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-N-2-((pyridin-2-yl)carbonyl)-3-((1-propylbutyl)sulfonyl))-D,L-alaninamide hydrochloride	686
	N-1-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-N-2-((3-hydroxybenzoyl)-3-((1-propylbutyl)sulfonyl))-D,L-alaninamide	688

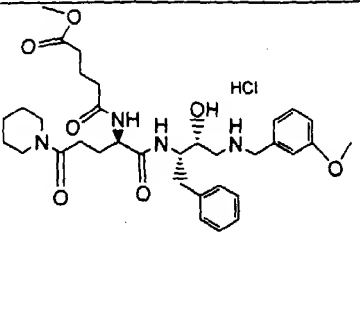
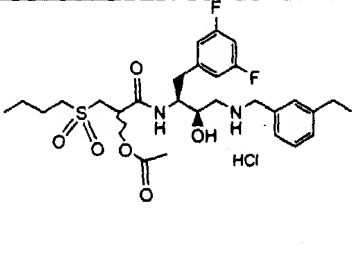
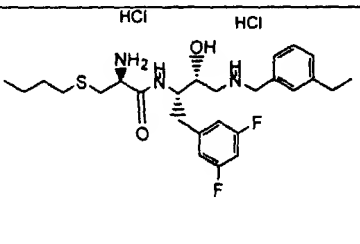
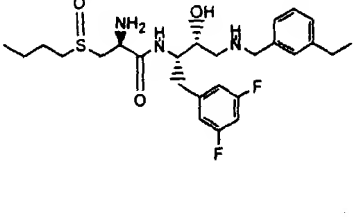
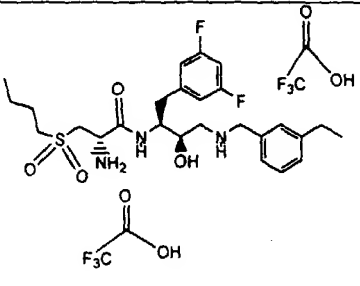
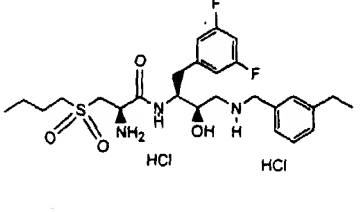
	N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N-2--(3-methylbenzoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride	686
	N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N-2--(3-ethylbenzoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide	700
	N-2--(3-chlorobenzoyl)-N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride	706
	N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N-2--(4-methylbenzoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride	686
	N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N-2--(4-methoxybenzoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-	702

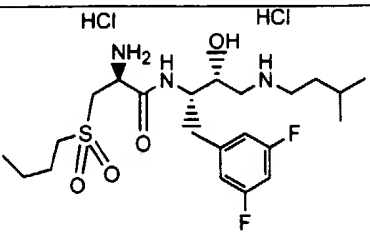
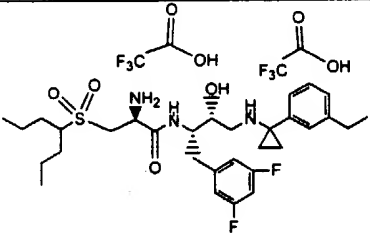
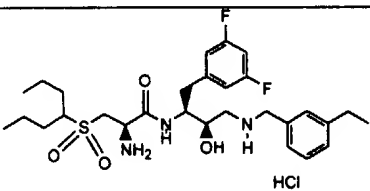
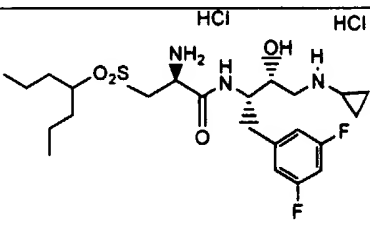
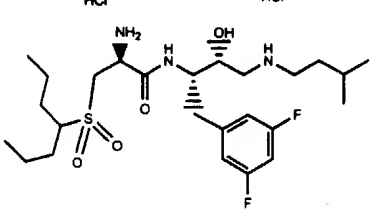
	alaninamide hydrochloride	
	N-1-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-N-2-((4-trifluoromethylbenzoyl)-3-((1-propylbutyl)sulfonyl))-D,L-alaninamide hydrochloride	740
	N-2-((cyclohexylcarbonyl)-N-1-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-3-((1-propylbutyl)sulfonyl))-D,L-alaninamide hydrochloride	678
	N-2-(benzoyl)-N-1-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-3-((1-propylbutyl)sulfonyl))-D,L-alaninamide	672
	N-2-(benzoyl)-N-1-((1S,2R)-3-(cyclopropylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl)-3-((1-propylbutyl)sulfonyl))-D,L-alaninamide hydrochloride	594
	N-1-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-N-2-((phenylacetyl)-3-((1-propylbutyl)sulfonyl))-D,L-alaninamide	686

	N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N-2--(3-phenylpropanoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide trifluoroacetate	700
	N-(3-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)amino)-3-oxo-2-[(1-propylbutyl)sulfonyl]methyl}propyl)benzamide	686
	N-1--{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N-2--(cyclopropylacetyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride	616
	N-1--{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N-2--[(methylsulfonyl)acetyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide trifluoroacetate	654
	N-1--{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N-2--[(methylthio)acetyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride	622

	<p>N-1--((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-N-2--(4-hydroxy-4-oxobutanoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride</p>	634
	<p>N-1--((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-N-2--[4-(methylamino)-4-oxobutanoyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride</p>	647
	<p>N-1--((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-N-2--(4-methoxy-4-oxobutanoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride</p>	648
	<p>N-(methanesulfonyl)glycyl-N-1--((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide hydrochloride</p>	669
	<p>N-2--acetyl-N-1--((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-3-(phenylsulfonyl)-D,L-alaninamide hydrochloride</p>	554

	N-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-(2S)-2-[(4-methoxy-4-oxobutanoyl)amino]-5-oxo-5-piperidin-1-ylpentanamide hydrochloride	611
	(2R)-2-[[[(benzyloxy)carbonyl]amino]-N-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-5-oxo-5-piperidin-1-ylpentanamide hydrochloride	631
	N-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-(2R)-2-[(3-ethoxy-3-oxopropanoyl)amino]-5-oxo-5-piperidin-1-ylpentanamide hydrochloride	611
	N-1-((1S,2R)-1-benzyl-3-[(3-methoxybenzyl)amino]-2-hydroxypropyl)-N-2-((4-methoxy-4-oxobutanoyl)-N-5,5-dipropyl-D-glutamamide hydrochloride	627
	N-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-(2R)-2-[(4-methoxy-4-oxobutanoyl)amino]-5-oxo-5-piperidin-1-ylpentanamide hydrochloride	611

	N-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-(2R)-2-[(5-methoxy-5-oxopentanoyl)amino]-5-oxo-5-piperidin-1-ylpentanamide hydrochloride	625
	2-N-1-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-1-[(butylsulfonyl)methyl]-2-oxoethyl acetate	569
	S-butyl-N-1-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-D-cysteinamide dihydrochloride	494
	3-(butylsulfinyl)-N-1-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-D-alaninamide	510
	3-(butylsulfonyl)-N-1-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-D-alaninamide bis(trifluoroacetate)	526
	3-(butylsulfonyl)-N-1-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-L-alaninamide	526

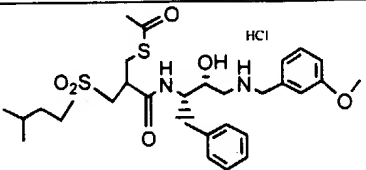
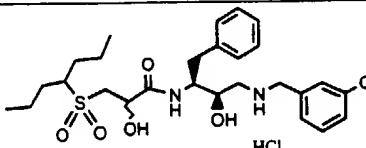
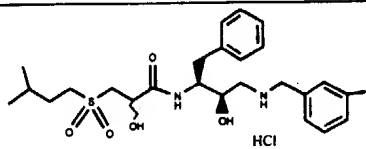
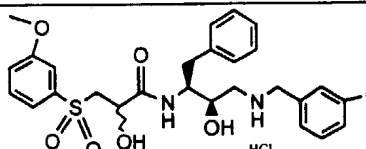
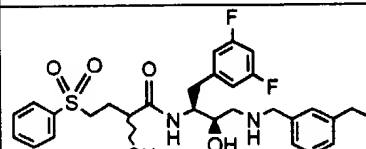
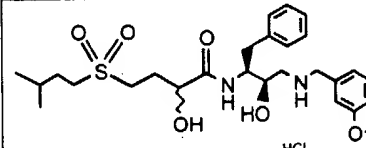
	dihydrochloride	
	3-(butylsulfonyl)-N-1- [(1S,2R)-1-(3,5- difluorobenzyl)-2-hydroxy-3- (isopentylamino)propyl]-D- alaninamide dihydrochloride	478
	N-1-[(1S,2R)-1-(3,5- difluorobenzyl)-3-[[1-(3- ethylphenyl)cyclopropyl]amino] -2-hydroxypropyl)-3-[(1- propylbutyl)sulfonyl]-D- alaninamide bis(trifluoroacetate)	594
	N-1-[(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl)-3-[(1- propylbutyl)sulfonyl]-L- alaninamide dihydrochloride	568
	N-1-[(1S,2R)-3- (cyclopropylamino)-1-(3,5- difluorobenzyl)-2- hydroxypropyl)-3-[(1- propylbutyl)sulfonyl]-D- alaninamide dihydrochloride	490
	N-1-[(1S,2R)-1-(3,5- difluorobenzyl)-2- hydroxypropyl)-3- (isopentylamino)]-3-[(1- propylbutyl)sulfonyl]-D- alaninamide dihydrochloride	520

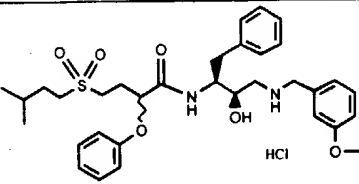
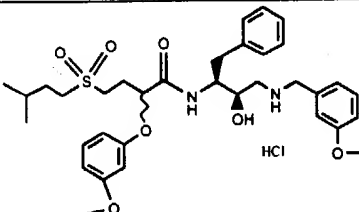
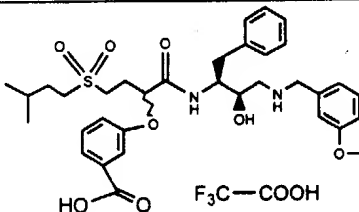
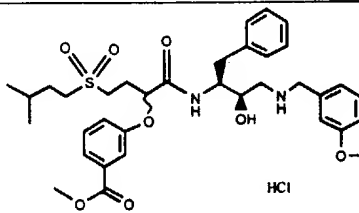
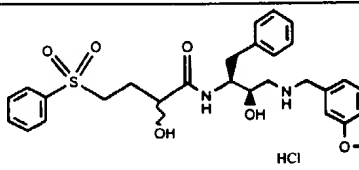
	N-1--((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide dihydrochloride	568
	N-1--((1S,2S)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]alaninamide hydrochloride	568
	N-1--((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N-2--(phenoxycetyl)-3-[(1-propylbutyl)sulfonyl]alaninamide hydrochloride	702
	N-2--[(5-chlorothiophen-2-yl)sulfonyl]-N-1--((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide	748
	N-1--((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N-2--(phenylsulfonyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide	708

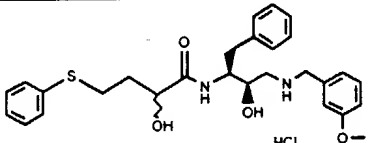
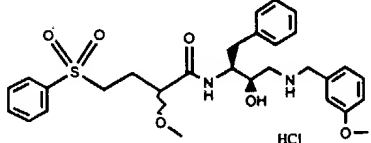
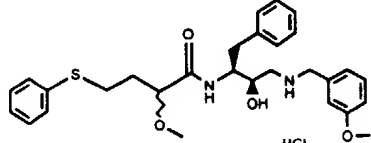
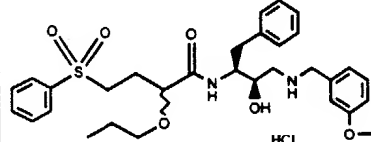
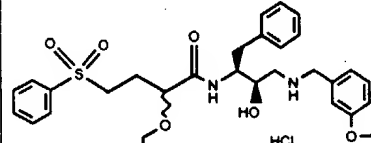
	<p>N-2-[(benzylamino)carbonyl]- N-1-[(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl]-3-[(1- propylbutyl)sulfonyl]-D,L- alaninamide</p>	701
	<p>4-[(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl]amino)-4-oxo-3- [(1- propylbutyl)sulfonyl]methyl]bu tanoic acid trifluoroacetate</p>	611
	<p>4-[(1S,2R)-1-benzyl-2- hydroxy-3-[(3- methoxybenzyl)amino]propyl]ami no)-3- [(isopentylsulfonyl)methyl]-4- oxobutanoic acid hydrochloride</p>	549
	<p>methyl 4-[(1S,2R)-1-benzyl-2- hydroxy-3-[(3- methoxybenzyl)amino]propyl]ami no)-3- [(isopentylsulfonyl)methyl]-4- oxobutanoate hydrochloride</p>	563
	<p>N-1-[(1S,2R)-1-benzyl-2- hydroxy-3-[(3- methoxybenzyl)amino]propyl]-2- [(isopentylsulfonyl)methyl]suc cinamide hydrochloride</p>	548

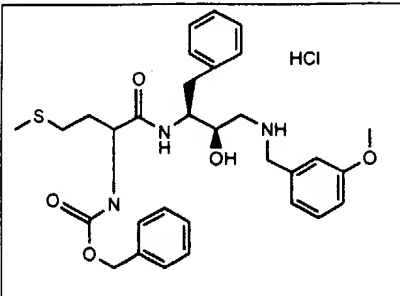
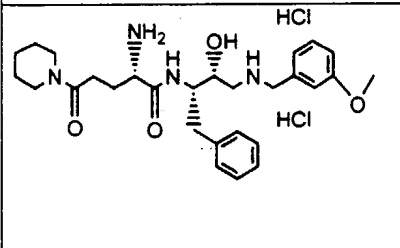
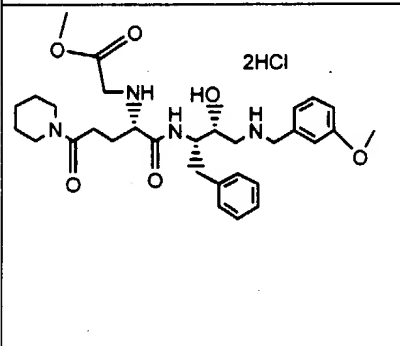
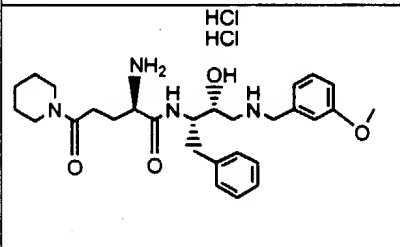
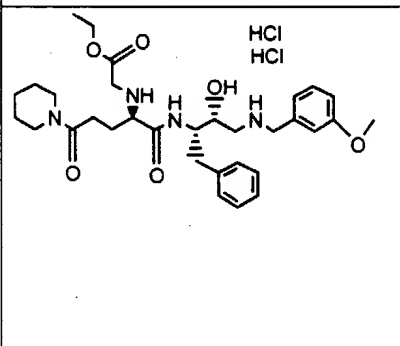
	<p>N-1-((1S,2R)-1-benzyl-2-hydroxy-3-((3-methoxybenzyl)amino)propyl)-2-((isopentylsulfonyl)methyl)-N-4-methylsuccinamide hydrochloride</p>	562
	<p>N-1-((1S,2R)-1-benzyl-2-hydroxy-3-((3-methoxybenzyl)amino)propyl)-2-((isopentylsulfonyl)methyl)-N-4,N-4-dimethylsuccinamide hydrochloride</p>	576
	<p>N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-3-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)-2-(((1-propylbutyl)sulfonyl)methyl)propanamide</p>	693
	<p>N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-3-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)-2-(((1-propylbutyl)sulfonyl)methyl)propanamide (first isomer)</p>	693

	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)-2-(((1-propylbutyl)sulfonyl)methyl)propanamide (second isomer)	693
	N-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-3-(ethylsulfonyl)-2-(((isobutylsulfonyl)amino)methyl)propanamide hydrochloride	598
	N-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-3-(ethylthio)-2-(((isobutylsulfonyl)amino)methyl)propanamide hydrochloride	566
	(2S)-N-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-2-[(isopentylsulfonyl)amino]-4-(methylsulfonyl)butanamide hydrochloride	598
	N-1-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-N-2-((isopentylsulfonyl)-L-methioninamide hydrochloride	566

	S-{3-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)amino)-2-[(isopentylsulfonyl)methyl]-3-oxopropyl} ethanethioate hydrochloride	579
	N-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-2-hydroxy-3-[(1-propylbutyl)sulfonyl]propanamide	535
	N-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-2-hydroxy-3-(isopentylsulfonyl)propanamide hydrochloride	507
	N-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-2-hydroxy-3-(3-methoxyphenyl)sulfonylpropanamide hydrochloride	543
	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-hydroxy-4-(phenylsulfonyl)butanamide	561
	N-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-2-hydroxy-4-(phenylsulfonyl)butanamide hydrochloride	521

	(isopentylsulfonyl)butanamide hydrochloride	
	N-((1S,2R)-1-benzyl-2-hydroxy-3-((3-methoxybenzyl)amino)propyl)-4-(isopentylsulfonyl)-2-phenoxybutanamide hydrochloride	597
	N-((1S,2R)-1-benzyl-2-hydroxy-3-((3-methoxybenzyl)amino)propyl)-4-(isopentylsulfonyl)-2-(3-methoxyphenoxy)butanamide hydrochloride	627
	3-[1-(((1S,2R)-1-benzyl-2-hydroxy-3-((3-methoxybenzyl)amino)propyl)amino)carbonyl]-3-(isopentylsulfonyl)propoxybenzoic acid trifluoroacetate	641
	methyl 3-[1-(((1S,2R)-1-benzyl-2-hydroxy-3-((3-methoxybenzyl)amino)propyl)amino)carbonyl]-3-(isopentylsulfonyl)propoxybenzoate hydrochloride	655
	N-((1S,2R)-1-benzyl-2-hydroxy-3-((3-methoxybenzyl)amino)propyl)-2-hydroxy-4-(phenylsulfonyl)butanamide hydrochloride	527

	N-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-2-hydroxy-4-(phenylthio)butanamide hydrochloride	495
	N-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-2-methoxy-4-(phenylsulfonyl)butanamide hydrochloride	541
	N-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-2-methoxy-4-(phenylthio)butanamide hydrochloride	509
	N-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-4-(phenylsulfonyl)-2-propoxybutanamide hydrochloride	569
	N-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-2-(benzyloxy)-4-(phenylsulfonyl)butanamide hydrochloride	617

	<p>N-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-N-2-[(benzyloxy)carbonyl]-D,L-methioninamide hydrochloride</p>	566
	<p>(2S)-2-amino-N-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-5-oxo-5-piperidin-1-ylpentanamide dihydrochloride</p>	497
	<p>N-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-(2S)-2-[(2-ethoxy-2-oxoethyl)amino]-5-oxo-5-piperidin-1-ylpentanamide dihydrochloride</p>	569
	<p>(2R)-2-amino-N-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-5-oxo-5-piperidin-1-ylpentanamide dihydrochloride</p>	497
	<p>N-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-(2R)-2-[(2-ethoxy-2-oxoethyl)amino]-5-oxo-5-piperidin-1-ylpentanamide dihydrochloride</p>	583

	<p>N-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-(2R)-2-[(4-ethoxy-4-oxobutanyl)amino]-5-oxo-5-piperidin-1-ylpentanamide ditrifluoroacetate</p>	611
	<p>methyl (1R)-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]amino)carbonyl]-3-oxoheptylcarbamate</p>	
	<p>4-butyl-N-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-N-2-(methoxycarbonyl)-D-homoserinamide</p>	
	<p>3-(2-butyl-1,3-dioxolan-2-yl)-N-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-N-2-(methoxycarbonyl)-D-alaninamide</p>	
	<p>3-(2-butyl-1,3-dioxan-2-yl)-N-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-N-2-(methoxycarbonyl)-D-alaninamide</p>	

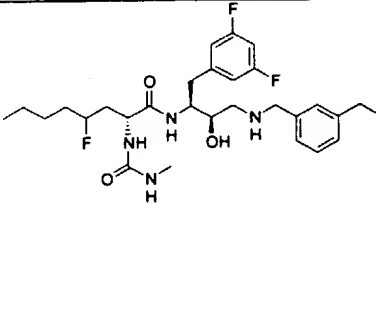
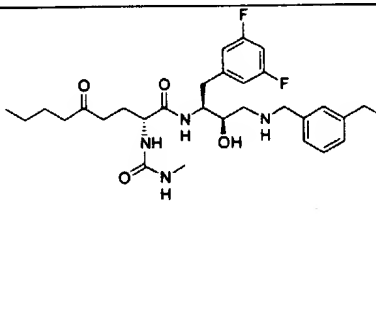
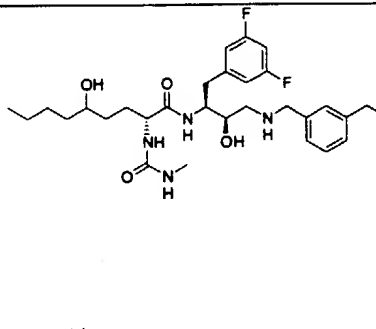
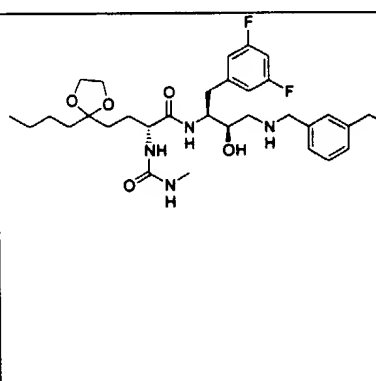
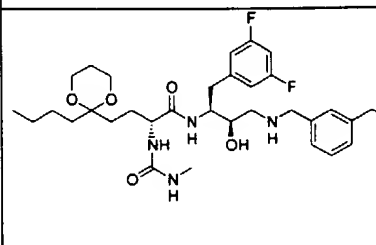
	methyl (1R)-1-(((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)amino)carbonyl]-3,3-difluoroheptylcarbamate	
	methyl (1R)-1-(((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)amino)carbonyl]-3-fluoroheptylcarbamate	
	methyl (1R)-1-(((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)amino)carbonyl]-4-oxooctylcarbamate	
	methyl (1R)-1-(((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)amino)carbonyl]-4-hydroxyoctylcarbamate	
	methyl (1R)-3-(2-butyl-1,3-dioxolan-2-yl)-1-(((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)amino)carbonyl]propylcarbamate	
	methyl (1R)-3-(2-butyl-1,3-dioxan-2-yl)-1-(((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)amino)carbonyl]propylcarbamate	

	methyl (1R)-1-((((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)amino)carbonyl)-4-fluorooctylcarbamate	
	methyl (1R)-1-((((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)amino)carbonyl)-4,4-difluorooctylcarbamate	
	3-(butylsulfonyl)-N-1-((((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethynylbenzyl)amino)-2-hydroxypropyl)amino)-N-2-(methoxycarbonyl)-D-alaninamide	
	3-(butylsulfonyl)-N-1-((((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((3-(trifluoromethyl)benzyl)amino)propyl)amino)-N-2-(methoxycarbonyl)-D-alaninamide	
	3-(butylsulfonyl)-N-1-((((1S,2R)-1-(3,5-difluorobenzyl)-3-([1-(3-ethylphenyl)cyclopropyl]amino)-2-hydroxypropyl)amino)-N-2-(methoxycarbonyl)-D-alaninamide	

	<p>3-(butylsulfonyl)-N-1-- ((1S,2R)-1-(3,5- difluorobenzyl)-3-({1-(3- ethynylphenyl)cyclopropyl}amin o)-2-hydroxypropyl)- N-2~(methoxycarbonyl)-D- alaninamide</p>	
	<p>3-(butylsulfonyl)-N-1-- [(1S,2R)-1-(3,5- difluorobenzyl)-2-hydroxy-3- ({1-[3- (trifluoromethyl)phenyl]cyclop ropropyl}amino)propyl]- N-2~(methoxycarbonyl)-D- alaninamide</p>	
	<p>N-((1R)-3-(butylsulfonyl)-1- [(((1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethynylbenzyl)amino]-2- hydroxypropyl)amino)carbonyl]p ropropyl)-3-methyl-1H-pyrazole-5- carboxamide</p>	
	<p>N-((1R)-3-(butylsulfonyl)-1- [(((1S,2R)-1-(3,5- difluorobenzyl)-2-hydroxy-3- {3- (trifluoromethyl)benzyl}amino} propyl)amino)carbonyl]propyl)- 3-methyl-1H-pyrazole-5- carboxamide</p>	

	N-((1R)-3-(butylsulfonyl)-1- {(((1S,2R)-1-(3,5- difluorobenzyl)-3-([1-(3- ethylphenyl)cyclopropyl]amino) -2- hydroxypropyl)amino]carbonyl)p ropyl)-3-methyl-1H-pyrazole-5- carboxamide	
	N-((1R)-3-(butylsulfonyl)-1- {(((1S,2R)-1-(3,5- difluorobenzyl)-3-([1-(3- ethynylphenyl)cyclopropyl]amin o)-2- hydroxypropyl)amino]carbonyl)p ropyl)-3-methyl-1H-pyrazole-5- carboxamide	
	N-[(1R)-3-(butylsulfonyl)-1- {(((1S,2R)-1-(3,5- difluorobenzyl)-2-hydroxy-3- ([1-(3- (trifluoromethyl)phenyl)cyclop ropyl]amino)propyl]amino)carbo nyl)propyl]-3-methyl-1H- pyrazole-5-carboxamide	
	(2R)-N-((1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl)-2- {[(methylamino)carbonyl]amino} -4-oxooctanamide	

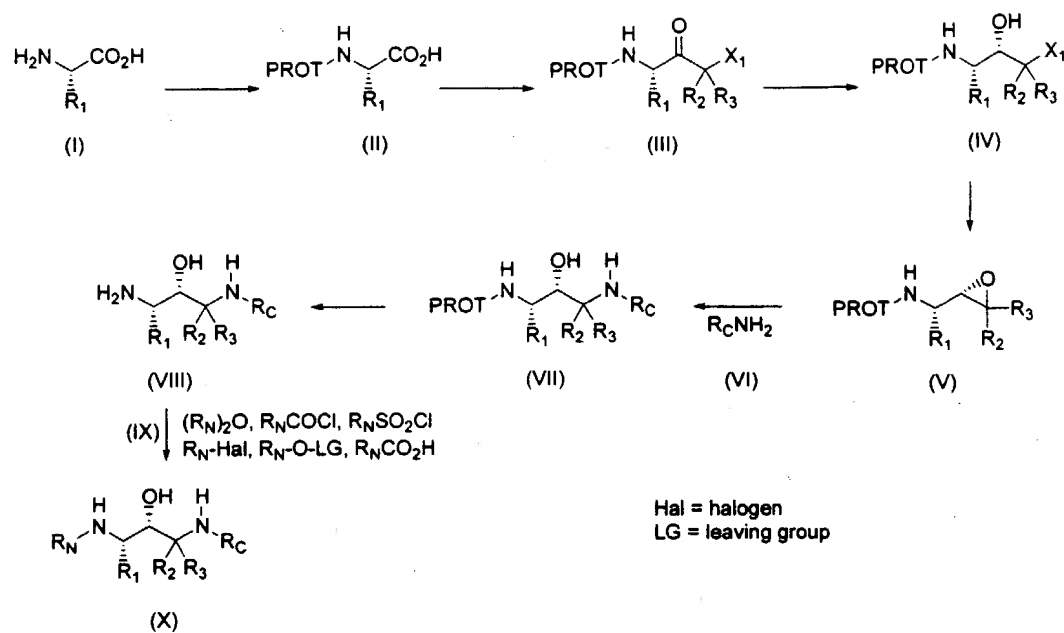
	4-butyl- N^1 -{((1 <i>S</i> ,2 <i>R</i>)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)- N^2 -[(methylamino)carbonyl]-D-homoserinamide	
	3-(2-butyl-1,3-dioxolan-2-yl)- N^1 -{((1 <i>S</i> ,2 <i>R</i>)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)- N^2 -[(methylamino)carbonyl]-D-alaninamide	
	3-(2-butyl-1,3-dioxan-2-yl)- N^1 -{((1 <i>S</i> ,2 <i>R</i>)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)- N^2 -[(methylamino)carbonyl]-D-alaninamide	
	(2 <i>R</i>)- N -{((1 <i>S</i> ,2 <i>R</i>)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4,4-difluoro-2-[(methylamino)carbonyl]amino) octanamide	

	(2R)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-4-fluoro-2-((methylamino)carbonyl)amino)octanamide	
	(2R)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-((methylamino)carbonyl)amino)-5-oxononanamide	
	(2R)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-5-hydroxy-2-((methylamino)carbonyl)amino)nonanamide	
	(2R)-4-(2-butyl-1,3-dioxolan-2-yl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-((methylamino)carbonyl)amino)butanamide	
	(2R)-4-(2-butyl-1,3-dioxan-2-yl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-2-((methylamino)carbonyl)amino)butanamide	

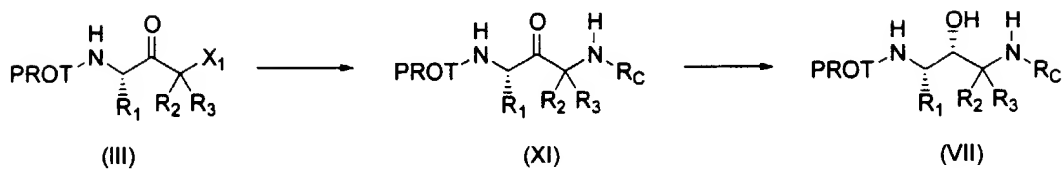
	{[(methylamino)carbonyl]amino} butanamide	
	(2R)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-5-fluoro-2-{[(methylamino)carbonyl]amino}nonanamide	
	(2R)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethylbenzyl)amino)-2-hydroxypropyl)-5,5-difluoro-2-{[(methylamino)carbonyl]amino}nonanamide	
	3-(butylsulfonyl)-N¹-((1S,2R)-1-(3,5-difluorobenzyl)-3-((3-ethynylbenzyl)amino)-2-hydroxypropyl)-N²-[(methylamino)carbonyl]-D-alaninamide.	
	3-(butylsulfonyl)-N¹-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-([3-(trifluoromethyl)benzyl]amino)propyl)-N²-[(methylamino)carbonyl]-D-alaninamide	

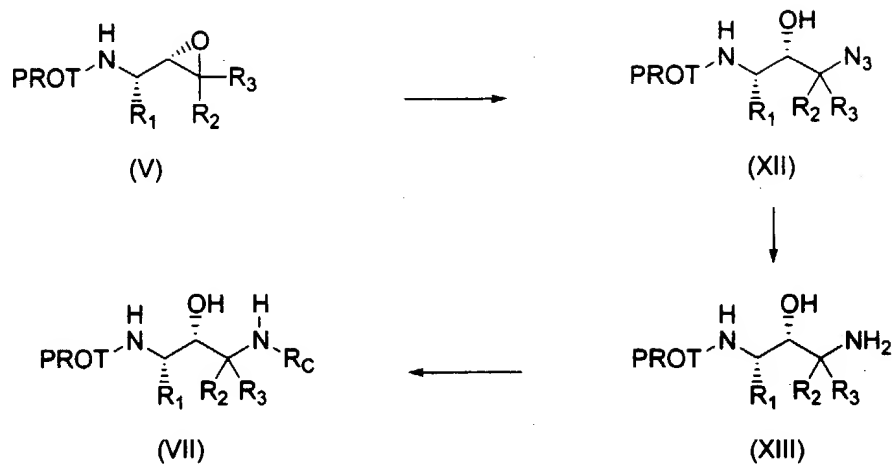
	<p>3-(butylsulfonyl)-N^1-((1<i>S</i>,2<i>R</i>)-1-(3,5-difluorobenzyl)-3-((1-(3-ethylphenyl)cyclopropyl)amino)-2-hydroxypropyl)-N^2-[(methylamino)carbonyl]-D-alaninamide</p>	
	<p>3-(butylsulfonyl)-N^1-((1<i>S</i>,2<i>R</i>)-1-(3,5-difluorobenzyl)-3-((1-(3-ethynylphenyl)cyclopropyl)amino)-2-hydroxypropyl)-N^2-[(methylamino)carbonyl]-D-alaninamide</p>	
	<p>3-(butylsulfonyl)-N^1-[(1<i>S</i>,2<i>R</i>)-1-(3,5-difluorobenzyl)-2-hydroxy-3-((1-[3-(trifluoromethyl)phenyl]cyclopropyl)amino)propyl]-N^2-[(methylamino)carbonyl]-D-alaninamide</p>	
	<p>4-Methyl-pyrazole-1-carboxylic acid {2-(butane-1-sulfonyl)-1-[1-(3,5-difluoro-benzyl)-3-(3-ethynyl-benzylamino)-2-hydroxy-propylcarbamoyl]-ethyl}-amide</p>	

	<p>4-Methyl-pyrazole-1-carboxylic acid (2-(butane-1-sulfonyl)-1-[1-(3,5-difluoro-benzyl)-2-hydroxy-3-(3-(3-trifluoromethyl-benzylamino)-propylcarbamoyl]-ethyl)-amide</p>	
	<p>4-Methyl-pyrazole-1-carboxylic acid (2-(butane-1-sulfonyl)-1-{1-(3,5-difluoro-benzyl)-3-[1-(3-ethyl-phenyl)-cyclopropylamino]-2-hydroxy-propylcarbamoyl}-ethyl)-amide</p>	
	<p>4-Methyl-pyrazole-1-carboxylic acid (2-(butane-1-sulfonyl)-1-{1-(3,5-difluoro-benzyl)-3-[1-(3-ethyny-1-phenyl)-cyclopropylamino]-2-hydroxy-propylcarbamoyl}-ethyl)-amide</p>	
	<p>4-Methyl-pyrazole-1-carboxylic acid (2-(butane-1-sulfonyl)-1-{1-(3,5-difluoro-benzyl)-2-hydroxy-3-[1-(3-trifluoromethyl-phenyl)-cyclopropylamino]-propylcarbamoyl}-ethyl)-amide</p>	

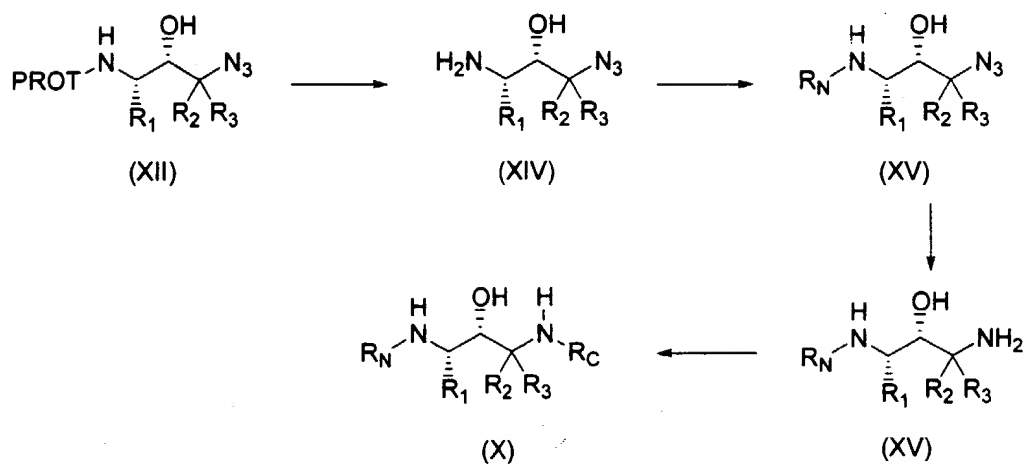
SCHEME A

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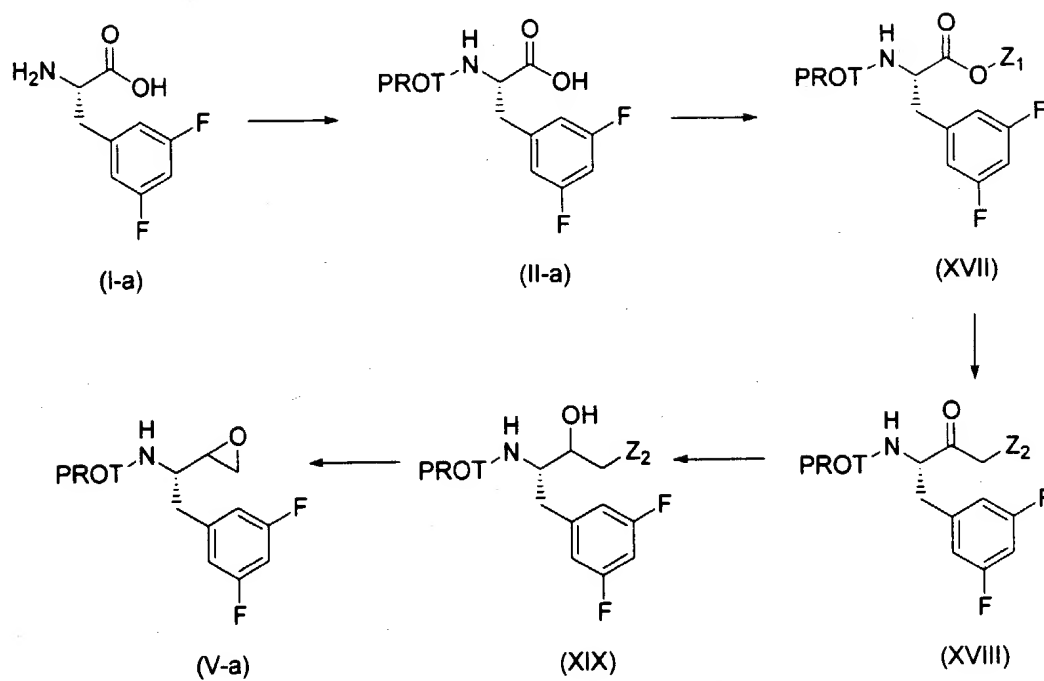
SCHEME B

SCHEME C

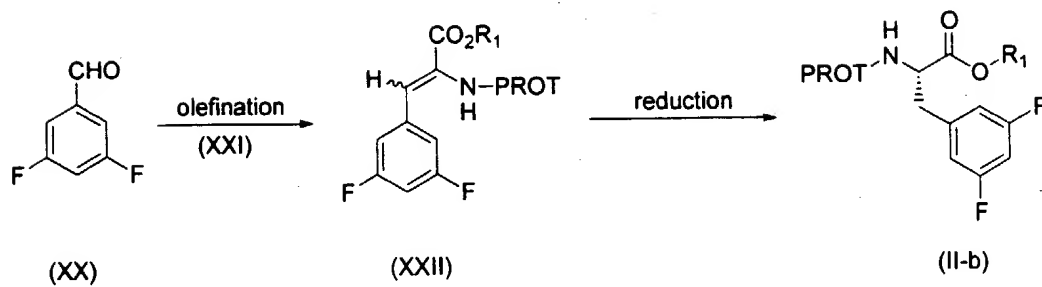
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SCHEME D

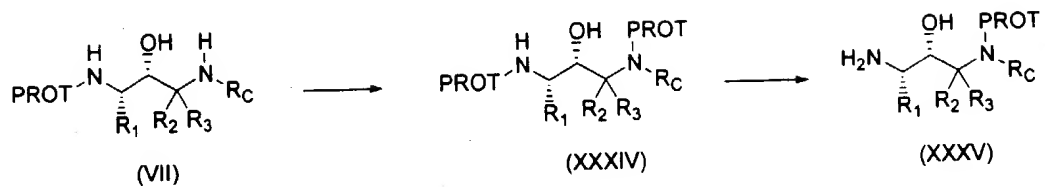
SCHEME E



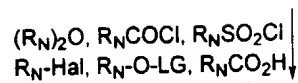
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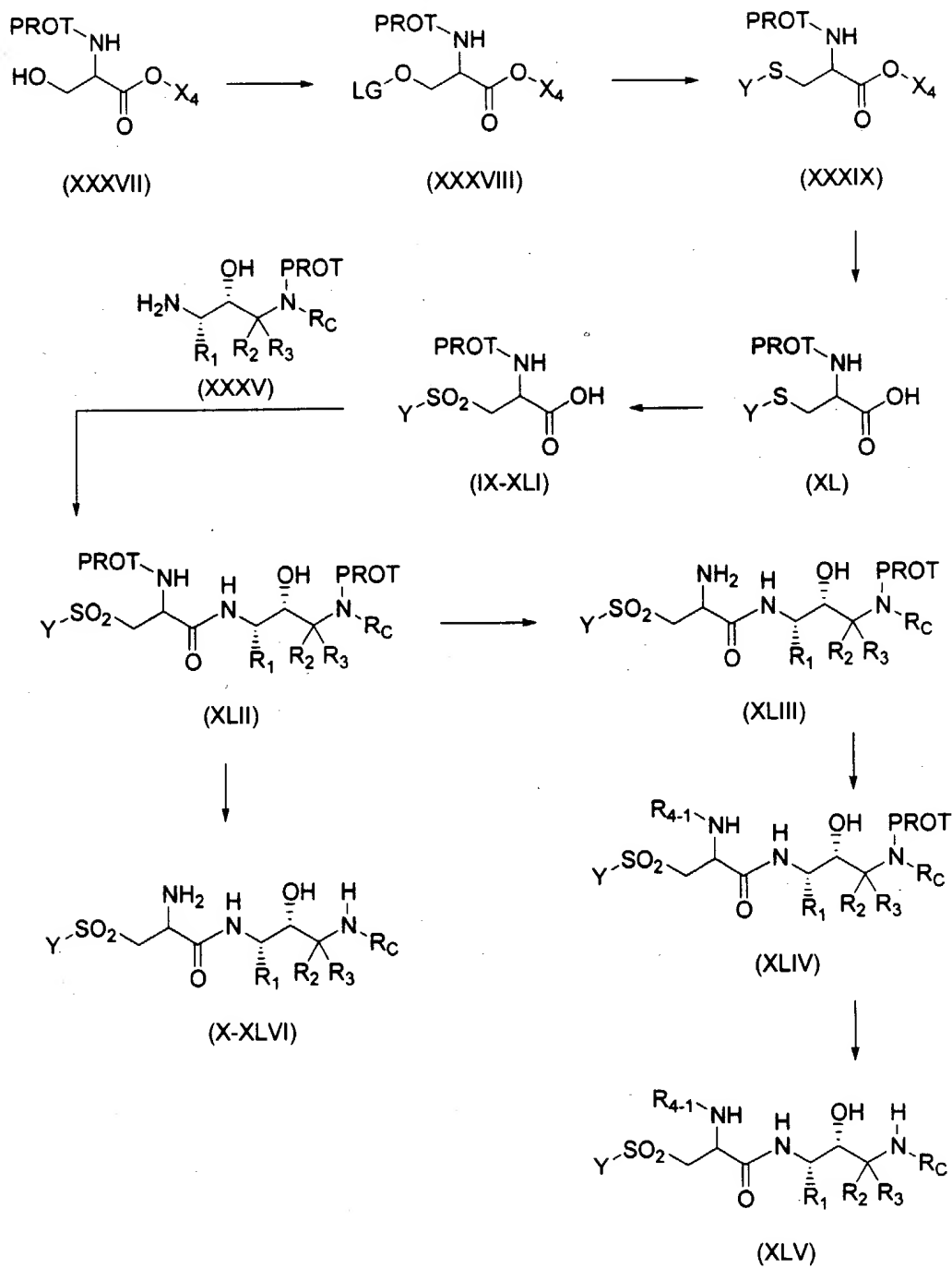


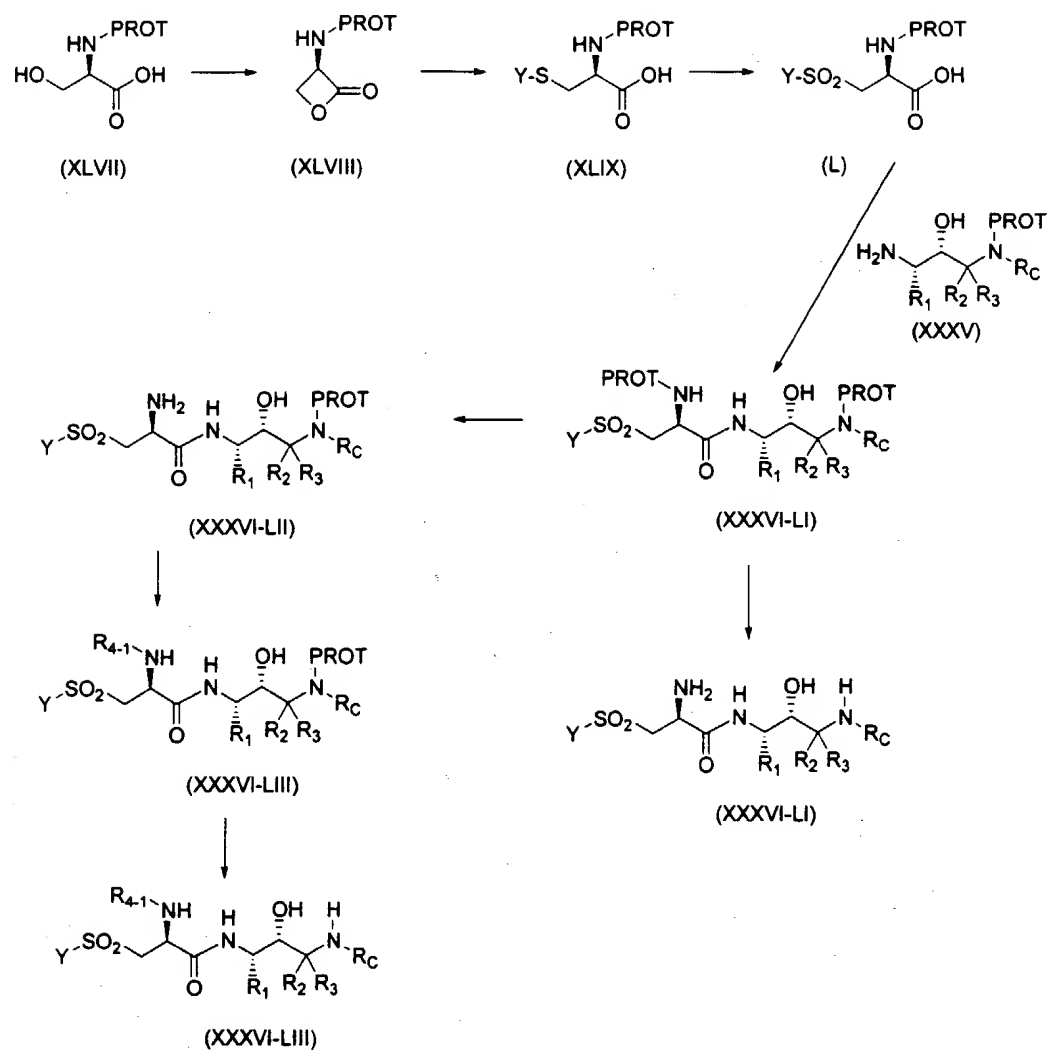
SCHEME G

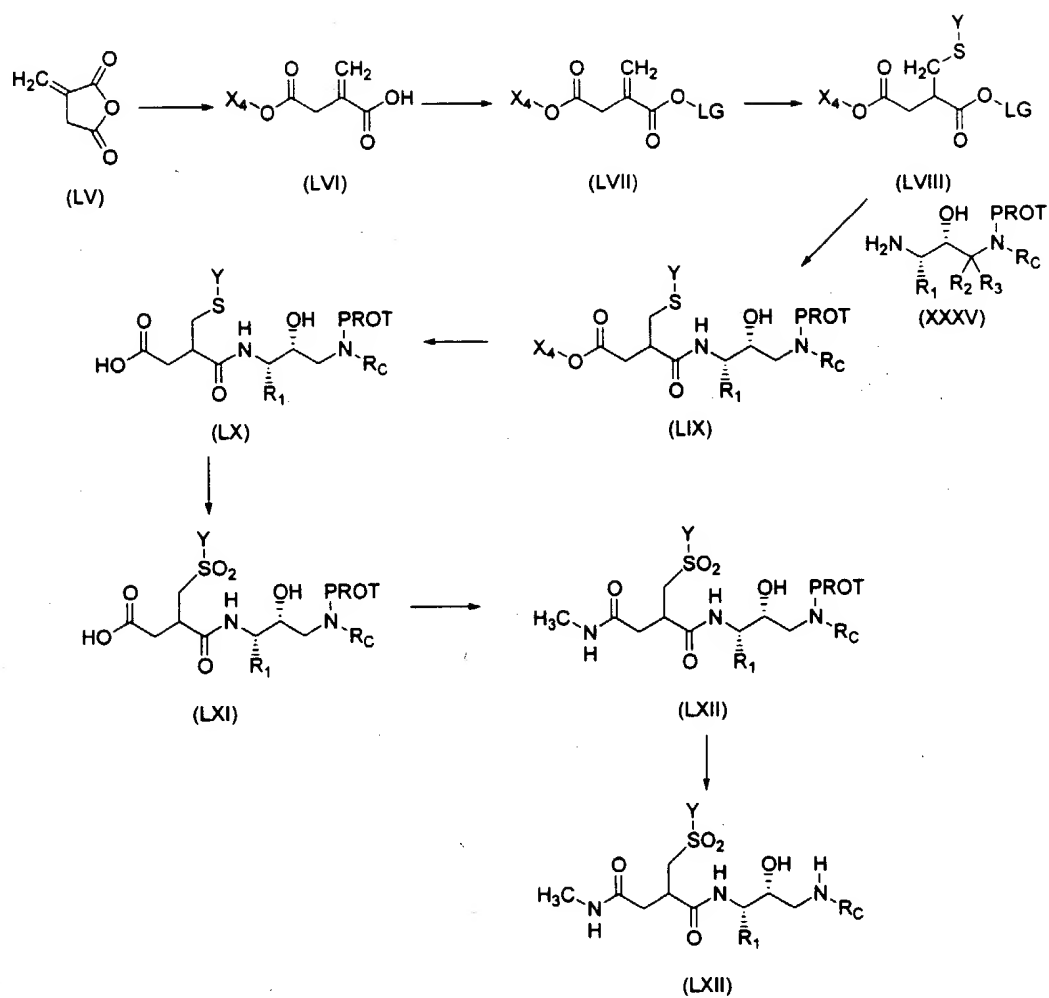


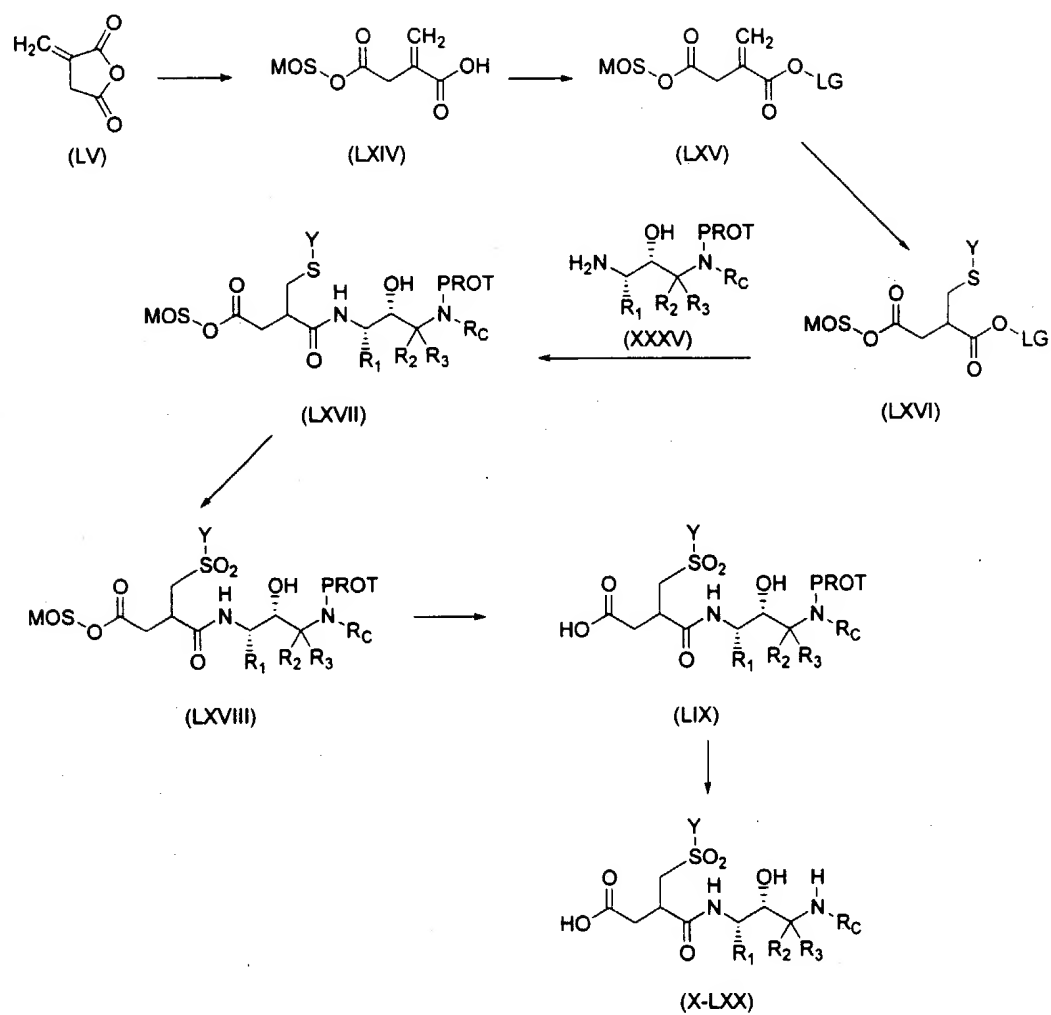
Hal = halogen
 LG = leaving group



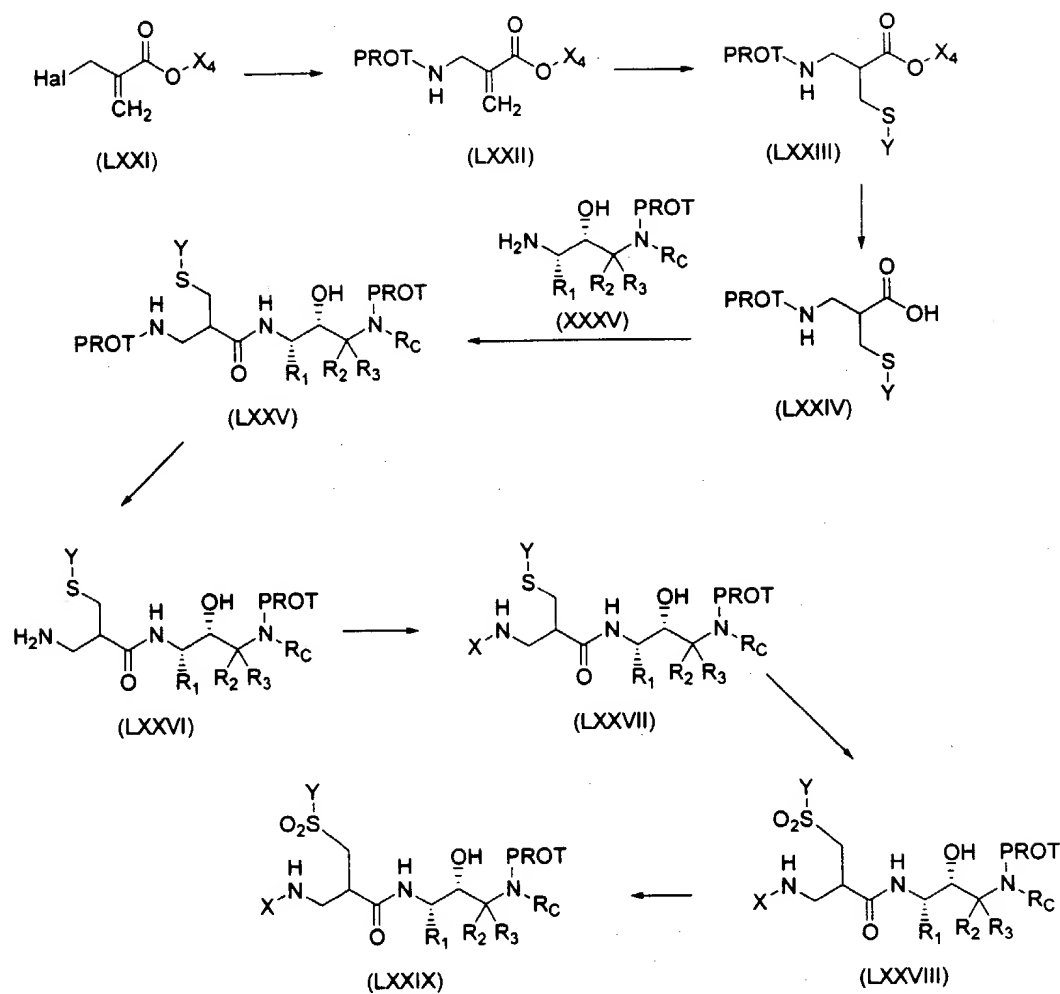
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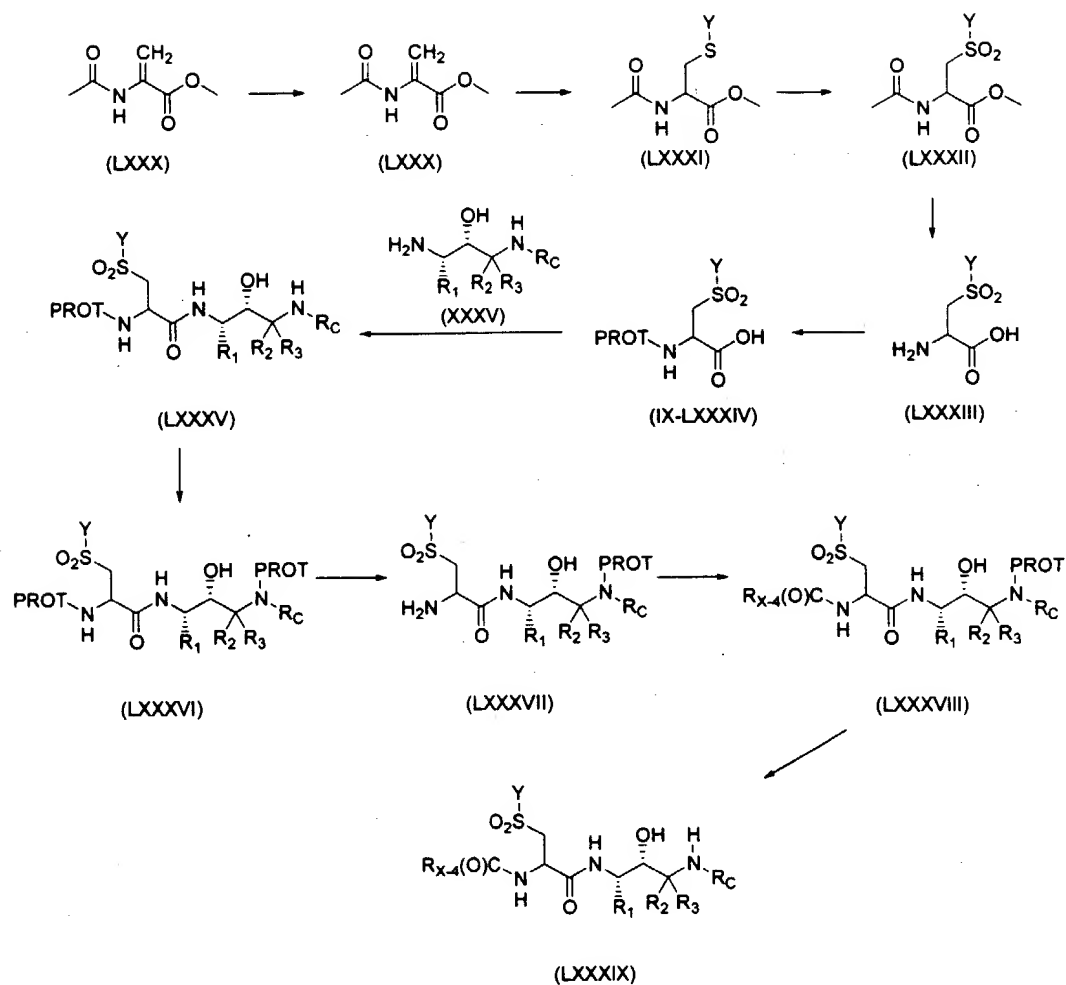
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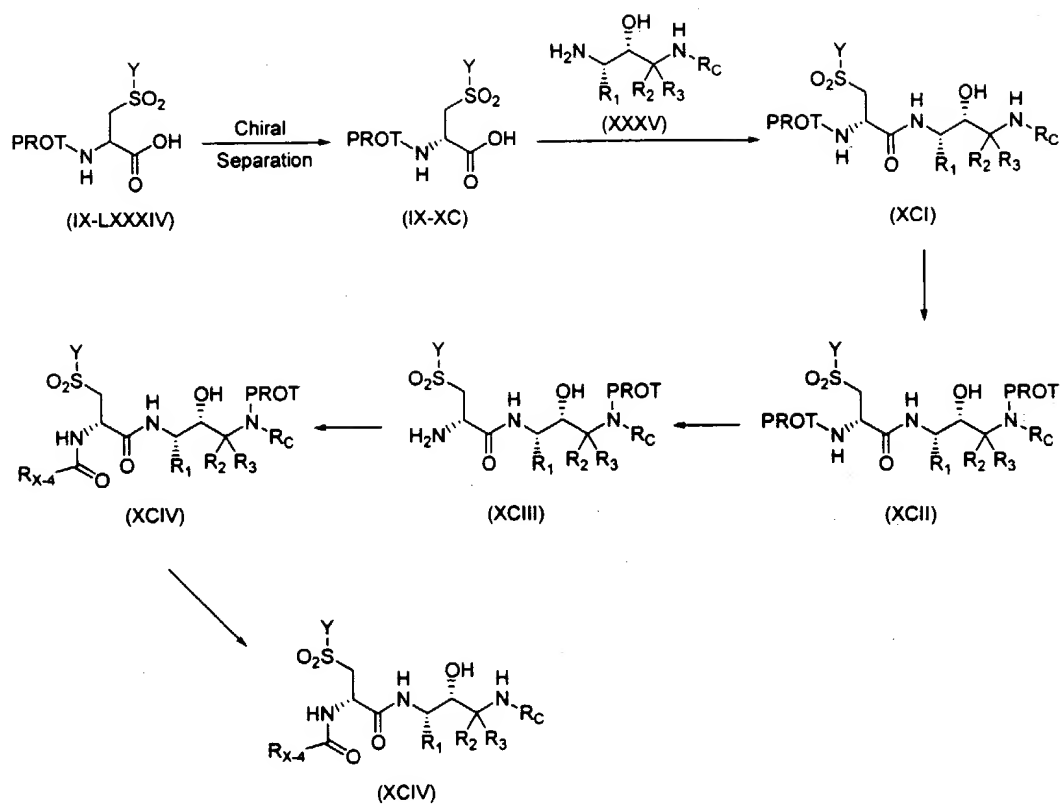
SCHEME J

SCHEME K

SCHEME L

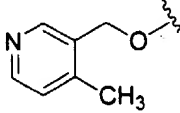
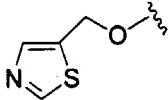
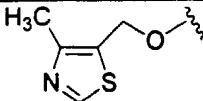
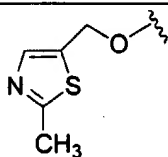
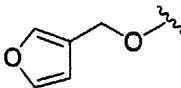
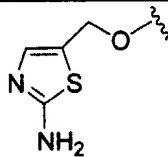
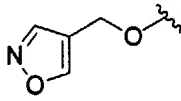
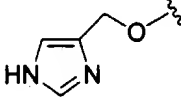
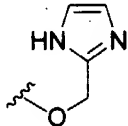
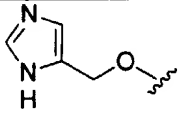
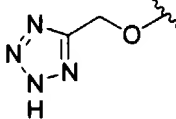


SCHEME M

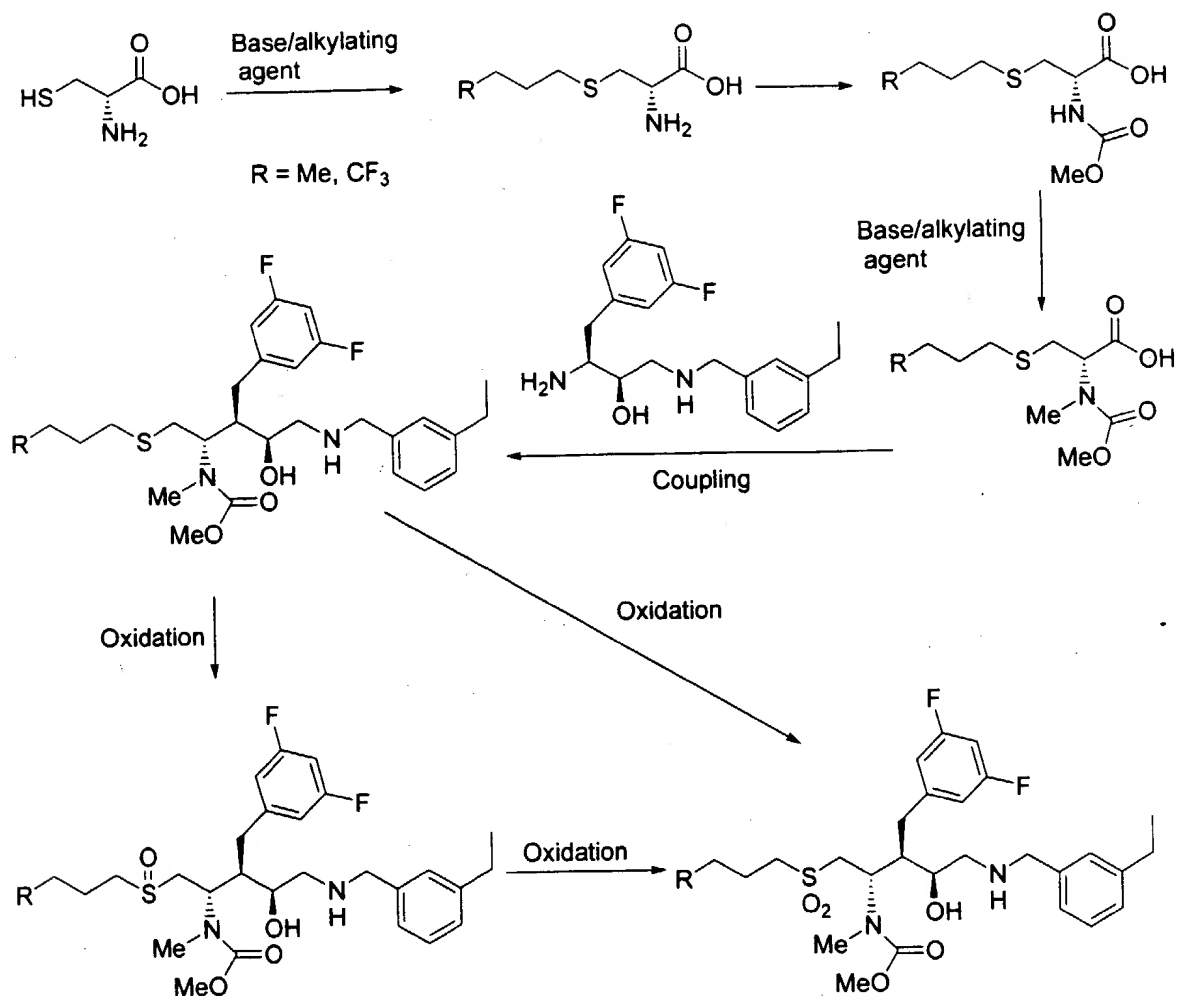
SCHEME NSCHEME O - Alcohols for Carbamate Formation

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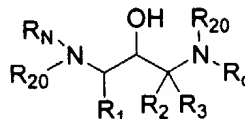
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SCHEME P

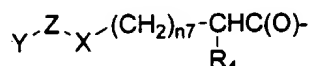


What is claimed is:

1. A compound of the formula:



- 5 or a pharmaceutically acceptable salt thereof, wherein
 R_N is:



wherein

- R_4 is selected from the group consisting of H; NH_2 ; $-NH-(CH_2)_{n6}-$
 10 R_{4-1} ; $-NHR_8$; $-NR_{50}C(O)R_5$; C_1-C_4 alkyl- $NHC(O)R_5$; $-(CH_2)_{0-4}R_8$; $-$
 $O-C_1-C_4$ alkanoyl; OH; C_6-C_{10} aryloxy optionally substituted
 with 1, 2, or 3 groups that are independently halogen, C_1-
 C_4 alkyl, $-CO_2H$, $-C(O)-C_1-C_4$ alkoxy, or C_1-C_4 alkoxy; C_1-C_6
 alkoxy; aryl C_1-C_4 alkoxy; $-NR_{50}CO_2R_{51}$; $-C_1-C_4$ alkyl-
 15 $NR_{50}CO_2R_{51}$; $-C\equiv N$; $-CF_3$; $-CF_2-CF_3$; $-C\equiv CH$; $-CH_2-CH=CH_2$; $-(CH_2)_{1-}$
 $4-R_{4-1}$; $-(CH_2)_{1-4}-NH-R_{4-1}$; $-O-(CH_2)_{n6}-R_{4-1}$; $-S-(CH_2)_{n6}-R_{4-1}$; $-$
 $(CH_2)_{0-4}-NHC(O)-(CH_2)_{0-6}-R_{52}$; $-(CH_2)_{0-4}-R_{53}-(CH_2)_{0-4}-R_{54}$;

wherein

- n_6 is 0, 1, 2, or 3;
 20 n_7 is 0, 1, 2, or 3;
 R_{4-1} is selected from the group consisting of $-SO_2-(C_1-C_8$
 alkyl); $-SO-(C_1-C_8$ alkyl); $-S-(C_1-C_8$ alkyl); $-S-CO-$
 $(C_1-C_6$ alkyl); $-SO_2-NR_{4-2}R_{4-3}$; $-CO-C_1-C_2$ alkyl; $-CO-NR_{4-}$
 $3R_{4-4}$;
 25 R_{4-2} and R_{4-3} are independently H, C_1-C_3 alkyl, or C_3-C_6
 cycloalkyl;
 R_{4-4} is alkyl, arylalkyl, alkanoyl, or arylalkanoyl;
 R_{4-6} is H or C_1-C_6 alkyl;
 R_5 is selected from the group consisting of C_3-C_7
 30 cycloalkyl; C_1-C_6 alkyl optionally substituted with
 1, 2, or 3 groups that are independently halogen, -

NR₆R₇, C₁-C₄ alkoxy, C₅-C₆ heterocycloalkyl, C₅-C₆ heteroaryl, C₆-C₁₀ aryl, C₃-C₇ cycloalkyl C₁-C₄ alkyl, -S-C₁-C₄ alkyl, -SO₂-C₁-C₄ alkyl, -CO₂H, -CONR₆R₇, -CO₂-C₁-C₄ alkyl, C₆-C₁₀ aryloxy; heteroaryl optionally substituted with 1, 2, or 3 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, C₁-C₄ haloalkyl, or OH; heterocycloalkyl optionally substituted with 1, 2, or 3 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, or C₂-C₄ alkanoyl; aryl optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, OH, C₁-C₄ alkyl, C₁-C₄ alkoxy, or C₁-C₄ haloalkyl; and -NR₆R₇; wherein

R₆ and R₇ are independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkanoyl, phenyl, -SO₂-C₁-C₄ alkyl, phenyl C₁-C₄ alkyl;

R₈ is selected from the group consisting of -SO₂-heteroaryl, -SO₂-aryl, -SO₂-heterocycloalkyl, -SO₂-C₁-C₁₀ alkyl, -C(O)NHR₉, heterocycloalkyl, -S-C₁-C₆ alkyl, -S-C₂-C₄ alkanoyl, wherein

R₉ is aryl C₁-C₄ alkyl, C₁-C₆ alkyl, or H;

R₅₀ is H or C₁-C₆ alkyl;

R₅₁ is selected from the group consisting of aryl C₁-C₄ alkyl; C₁-C₆ alkyl optionally substituted with 1, 2, or 3 groups that are independently halogen, cyano, heteroaryl, -NR₆R₇, -C(O)NR₆R₇, C₃-C₇ cycloalkyl, or -C₁-C₄ alkoxy; heterocycloalkyl optionally substituted with 1 or 2 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, C₂-C₄ alkanoyl, aryl C₁-C₄ alkyl, and -SO₂ C₁-C₄ alkyl; alkenyl; alkynyl; heteroaryl optionally substituted with 1, 2, or 3 groups that are independently OH, C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, NH₂, NH(C₁-C₆ alkyl) or N(C₁-C₆ alkyl)(C₁-C₆ alkyl); heteroarylalkyl optionally

substituted with 1, 2, or 3 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, NH₂, NH(C₁-C₆ alkyl) or N(C₁-C₆ alkyl)(C₁-C₆ alkyl); aryl; heterocycloalkyl; C₃-C₈ cycloalkyl; and cycloalkylalkyl; wherein the aryl, heterocycloalkyl, C₃-C₈ cycloalkyl, and cycloalkylalkyl groups are optionally substituted with 1, 2, 3, 4 or 5 groups that are independently halogen, CN, NO₂, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₂-C₆ alkanoyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, hydroxy, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy C₁-C₆ alkyl, C₁-C₆ thioalkoxy, C₁-C₆ thioalkoxy C₁-C₆ alkyl, or C₁-C₆ alkoxy C₁-C₆ alkoxy;

R₅₂ is heterocycloalkyl, heteroaryl, aryl, cycloalkyl, -S(O)₀₋₂-C₁-C₆ alkyl, CO₂H, -C(O)NH₂, -C(O)NH(alkyl), -C(O)N(alkyl)(alkyl), -CO₂-alkyl, -NHS(O)₀₋₂-C₁-C₆ alkyl, -N(alkyl)S(O)₀₋₂-C₁-C₆ alkyl, -S(O)₀₋₂-heteroaryl, -S(O)₀₋₂-aryl, -NH(arylalkyl), -N(alkyl)(arylalkyl), thioalkoxy, or alkoxy, each of which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, alkoxy, thioalkoxy, halogen, haloalkyl, haloalkoxy, alkanoyl, NO₂, CN, alkoxycarbonyl, or aminocarbonyl;

R₅₃ is absent, -O-, -C(O)-, -NH-, -N(alkyl)-, -NH-S(O)₀₋₂-, -N(alkyl)-S(O)₀₋₂-, -S(O)₀₋₂-NH-, -S(O)₀₋₂-N(alkyl)-, -NH-C(S)-, or -N(alkyl)-C(S)-;

R₅₄ is heteroaryl, aryl, arylalkyl, heterocycloalkyl, CO₂H, -CO₂-alkyl, -C(O)NH(alkyl), -C(O)N(alkyl)(alkyl), -C(O)NH₂, C₁-C₈ alkyl, OH, aryloxy, alkoxy, arylalkoxy, NH₂, NH(alkyl), N(alkyl)(alkyl), or -C₁-C₆ alkyl-CO₂-C₁-C₆ alkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently alkyl, alkoxy, CO₂H, -CO₂-alkyl, thioalkoxy, halogen, haloalkyl, haloalkoxy,

hydroxyalkyl, alkanoyl, NO₂, CN, alkoxycarbonyl, or aminocarbonyl;

X is selected from the group consisting of -C₁-C₆ alkylidenyl optionally optionally substituted with 1, 2, or 3 methyl groups; and -NR₄₋₆-; or

R₄ and R₄₋₆ combine to form -(CH₂)_{n10}-, wherein n₁₀ is 1, 2, 3, or 4;

Z is selected from the group consisting of a bond; SO₂; SO; S; and C(O);

Y is selected from the group consisting of H; C₁-C₄ haloalkyl; C₅-C₆ heterocycloalkyl; C₆-C₁₀ aryl; OH; -N(Y₁)(Y₂); C₁-C₁₀ alkyl optionally substituted with 1 thru 3 substituents which can be the same or different and are selected from the group consisting of halogen, hydroxy, alkoxy, thioalkoxy, and haloalkoxy; C₃-C₈ cycloalkyl optionally substituted with 1, 2, or 3 groups independently selected from C₁-C₃ alkyl, and halogen; alkoxy; aryl optionally substituted with halogen, alkyl, alkoxy, CN or NO₂; arylalkyl optionally substituted with halogen, alkyl, alkoxy, CN or NO₂; wherein

Y₁ and Y₂ are the same or different and are H; C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 substituents selected from the group consisting of halogen, C₁-C₄ alkoxy, C₃-C₈ cycloalkyl, and OH; C₂-C₆ alkenyl; C₂-C₆ alkanoyl; phenyl; -SO₂-C₁-C₄ alkyl; phenyl C₁-C₄ alkyl; or C₃-C₈ cycloalkyl C₁-C₄ alkyl; or

Y₁, Y₂ and the nitrogen to which they are attached form a ring selected from the group consisting of piperazinyl, piperidinyl, morpholinyl, and pyrrolidinyl, wherein each ring is optionally substituted with 1, 2, 3, or 4 groups that are independently C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkoxy C₁-C₆ alkyl, or halogen;

R₂₀ at each occurrence is independently selected from the group consisting of hydrogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkoxy C₁-C₆ alkyl, hydroxy C₁-C₆ alkyl, halo C₁-C₆ alkyl, C₁-C₆ alkanoyl, each of which is unsubstituted or substituted with 1, 2, 3, or 4 groups independently selected from halogen, alkyl, hydroxy, alkoxy, and NH₂, and -R₂₆-R₂₇, wherein

R₂₆ is selected from the group consisting of -C(O)-, -SO₂-, -CO₂-, -C(O)NH-, and -C(O)N(C₁-C₆ alkyl)-;

R₂₇ is selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, aryl C₁-C₆ alkyl, heterocycloalkyl, and heteroaryl, wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, haloalkyl, hydroxyalkyl, -C(O)NH₂, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)(C₁-C₆ alkyl), -C(O)NH(C₁-C₆ alkyl), -C(O)N(C₁-C₆ alkyl)(C₁-C₆ alkyl);

R₁ is -(CH₂)₁₋₂-S(O)₀₋₂-(C₁-C₆ alkyl), or

C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, OH, =O, -SH, -C≡N, -CF₃, -C₁-C₃ alkoxy, amino, mono- or dialkylamino, -N(R)C(O)R'-, -OC(=O)-amino and -OC(=O)-mono- or dialkylamino, or

C₂-C₆ alkenyl or C₂-C₆ alkynyl, each of which is optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, and mono- or dialkylamino, or

aryl, heteroaryl, heterocyclyl, -C₁-C₆ alkyl-aryl, -C₁-C₆ alkyl-heteroaryl, or -C₁-C₆ alkyl-heterocyclyl, where the ring portions of each are optionally substituted with 1, 2, 3, or 4 groups independently selected from halogen, -OH, -SH, -C≡N, -NR₁₀₅R'₁₀₅, -CO₂R, -N(R)COR', or -N(R)SO₂R', -C(=O)-(C₁-C₄) alkyl, -SO₂-amino, -SO₂-

mono or dialkylamino, -C(=O)-amino, -C(=O)-mono or dialkylamino, -SO₂-(C₁-C₄) alkyl, or

-C₁-C₆ alkoxy optionally substituted with 1, 2, or 3 groups which are independently a halogen, or

C₃-C₇ cycloalkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, -C₁-C₆ alkyl and mono- or dialkylamino, or

C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, -C₁-C₃ alkoxy, amino, mono- or dialkylamino and -C₁-C₃ alkyl, or

C₂-C₁₀ alkenyl or C₂-C₁₀ alkynyl each of which is optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, C₁-C₆ alkyl and mono- or dialkylamino; and

the heterocyclyl group is optionally further substituted with oxo;

R and R' independently are hydrogen or C₁-C₁₀ alkyl;

R₂ is selected from the group consisting of H; C₁-C₆ alkyl, optionally substituted with 1, 2, or 3 substituents that are independently selected from the group consisting of C₁-C₃ alkyl, halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, and -NR_{1-a}R_{1-b}; wherein

R_{1-a} and R_{1-b} are -H or C₁-C₆ alkyl;

-(CH₂)₀₋₄-aryl; -(CH₂)₀₋₄-heteroaryl; C₂-C₆ alkenyl; C₂-C₆ alkynyl; -CONR_{N-2}R_{N-3}; -SO₂NR_{N-2}R_{N-3}; -CO₂H; and -CO₂-(C₁-C₄ alkyl);

R₃ is selected from the group consisting of H; C₁-C₆ alkyl, optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of C₁-C₃ alkyl, halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, and -

$\text{NR}_{1-a}\text{R}_{1-b}$; $-(\text{CH}_2)_{0-4}\text{-aryl}$; $-(\text{CH}_2)_{0-4}\text{-heteroaryl}$; $\text{C}_2\text{-C}_6$ alkenyl;
 $\text{C}_2\text{-C}_6$ alkynyl; $-\text{CO-NR}_{N-2}\text{R}_{N-3}$; $-\text{SO}_2\text{-NR}_{N-2}\text{R}_{N-3}$; $-\text{CO}_2\text{H}$; and $-\text{CO-}$
 $\text{O-(C}_1\text{-C}_4\text{ alkyl)}$;

or

- 5 R_2 , R_3 and the carbon to which they are attached form a carbocycle of three thru seven carbon atoms, wherein one carbon atom is optionally replaced by a group selected from $-\text{O-}$, $-\text{S-}$, $-\text{SO}_2\text{-}$, or $-\text{NR}_{N-2}\text{-}$;

R_C is selected from the group consisting of $\text{C}_1\text{-C}_{10}$ alkyl

- 10 optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of R_{205} , $-\text{OC=ONR}_{235}\text{R}_{240}$, $-\text{S(=O)}_{0-2}(\text{C}_1\text{-C}_6\text{ alkyl})$, $-\text{SH}$, $-\text{NR}_{235}\text{C=ONR}_{235}\text{R}_{240}$, $-\text{C=ONR}_{235}\text{R}_{240}$, and $-\text{S(=O)}_2\text{NR}_{235}\text{R}_{240}$; $-(\text{CH}_2)_{0-3}\text{-(C}_3\text{-C}_8\text{)}$
 15 cycloalkyl wherein the cycloalkyl is optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of R_{205} , $-\text{CO}_2\text{H}$, and $-\text{CO}_2\text{-(C}_1\text{-C}_4\text{ alkyl)}$; $-(\text{CR}_{245}\text{R}_{250})_{0-4}\text{-aryl}$; $-(\text{CR}_{245}\text{R}_{250})_{0-4}\text{-heteroaryl}$; $-(\text{CR}_{245}\text{R}_{250})_{0-4}\text{-heterocycloalkyl}$; $-(\text{CR}_{245}\text{R}_{250})_{0-4}\text{-aryl-heteroaryl}$; $-(\text{CR}_{245}\text{R}_{250})_{0-4}\text{-aryl-heterocycloalkyl}$;
 20 $-(\text{CR}_{245}\text{R}_{250})_{0-4}\text{-aryl-aryl}$; $-(\text{CR}_{245}\text{R}_{250})_{0-4}\text{-heteroaryl-aryl}$; $-(\text{CR}_{245}\text{R}_{250})_{0-4}\text{-heteroaryl-heterocycloalkyl}$; $-(\text{CR}_{245}\text{R}_{250})_{0-4}\text{-heteroaryl-heteroaryl}$; $-(\text{CR}_{245}\text{R}_{250})_{0-4}\text{-heterocycloalkyl-heteroaryl}$; $-(\text{CR}_{245}\text{R}_{250})_{0-4}\text{-heterocycloalkyl-heterocycloalkyl}$; $-(\text{CR}_{245}\text{R}_{250})_{0-4}\text{-heterocycloalkyl-aryl}$;
 25 $-\text{[C(R}_{255}\text{)(R}_{260}\text{)]}_{1-3}\text{-CO-N-(R}_{255}\text{)}_2$; $-\text{CH(aryl)}_2$; $-\text{CH(heteroaryl)}_2$; $-\text{CH(heterocycloalkyl)}_2$; $-\text{CH(aryl)(heteroaryl)}$; cyclopentyl, cyclohexyl, or cycloheptyl ring fused to aryl, heteroaryl, or heterocycloalkyl wherein one carbon of the cyclopentyl, cyclohexyl, or cycloheptyl is
 30 optionally replaced with NH , NR_{215} , O , or S(=O)_{0-2} , and wherein the cyclopentyl, cyclohexyl, or cycloheptyl group can be optionally substituted with 1 or 2 groups that are independently R_{205} or $=\text{O}$; $-\text{CO-NR}_{235}\text{R}_{240}$; $-\text{SO}_2\text{-(C}_1\text{-C}_4\text{ alkyl)}$; $\text{C}_2\text{-C}_{10}$ alkenyl optionally substituted with 1, 2, or 3 R_{205}

groups; C₂-C₁₀ alkynyl optionally substituted with 1, 2, or 3 R₂₀₅ groups; -(CH₂)₀₋₁-CH((CH₂)₀₋₆-OH)-(CH₂)₀₋₁-aryl; -(CH₂)₀₋₁-CHRC₆-(CH₂)₀₋₁-heteroaryl; -CH(-aryl or -heteroaryl)-CO-O(C₁-C₄ alkyl); -CH(-CH₂-OH)-CH(OH)-phenyl-NO₂; (C₁-C₆ alkyl)-O-(C₁-C₆ alkyl)-OH; -CH₂-NH-CH₂-CH(-O-CH₂-CH₃)₂; -H; and -(CH₂)₀₋₆-C(=NR₂₃₅)(NR₂₃₅R₂₄₀); wherein each aryl is optionally substituted with 1, 2, or 3 R₂₀₀; each heteroaryl is optionally substituted with 1, 2, 3, or 4 R₂₀₀;

each heterocycloalkyl is optionally substituted with 1, 2, 3, or 4 R₂₁₀;

R₂₀₀ at each occurrence is independently selected from the group consisting of C₁-C₆ alkyl optionally substituted with 1, 2, or 3 R₂₀₅ groups; OH; -NO₂; halogen; -CO₂H; C≡N; -(CH₂)₀₋₄-CO-NR₂₂₀R₂₂₅; -(CH₂)₀₋₄-CO-(C₁-C₁₂ alkyl); -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkenyl); -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkynyl); -(CH₂)₀₋₄-CO-(C₃-C₇ cycloalkyl); -(CH₂)₀₋₄-CO-aryl; -(CH₂)₀₋₄-CO-heteroaryl; -(CH₂)₀₋₄-CO-heterocycloalkyl; -(CH₂)₀₋₄-CO₂R₂₁₅; -(CH₂)₀₋₄-SO₂-NR₂₂₀R₂₂₅; -(CH₂)₀₋₄-SO-(C₁-C₈ alkyl); -(CH₂)₀₋₄-SO₂-(C₁-C₁₂ alkyl); -(CH₂)₀₋₄-SO₂-(C₃-C₇ cycloalkyl); -(CH₂)₀₋₄-N(H or R₂₁₅)-CO₂R₂₁₅; -(CH₂)₀₋₄-N(H or R₂₁₅)-CO-N(R₂₁₅)₂; -(CH₂)₀₋₄-N-CS-N(R₂₁₅)₂; -(CH₂)₀₋₄-N(-H or R₂₁₅)-CO-R₂₂₀; -(CH₂)₀₋₄-NR₂₂₀R₂₂₅; -(CH₂)₀₋₄-O-CO-(C₁-C₆ alkyl); -(CH₂)₀₋₄-O-P(O)-(OR₂₄₀)₂; -(CH₂)₀₋₄-O-CO-N(R₂₁₅)₂; -(CH₂)₀₋₄-O-CS-N(R₂₁₅)₂; -(CH₂)₀₋₄-O-(R₂₁₅)₂; -(CH₂)₀₋₄-O-(R₂₁₅)₂-COOH; -(CH₂)₀₋₄-S-(R₂₁₅)₂; -(CH₂)₀₋₄-O-(C₁-C₆ alkyl optionally substituted with 1, 2, 3, or 5 -F); C₃-C₇ cycloalkyl; C₂-C₆ alkenyl optionally substituted with 1 or 2 R₂₀₅ groups; C₂-C₆ alkynyl optionally substituted with 1 or 2 R₂₀₅ groups; -(CH₂)₀₋₄-N(H or R₂₁₅)-SO₂-R₂₂₀; and -(CH₂)₀₋₄-C₃-C₇ cycloalkyl;

wherein each aryl group at each occurrence is optionally substituted with 1, 2, or 3 groups

that are independently R_{205} , R_{210} or C_1 - C_6 alkyl substituted with 1, 2, or 3 groups that are independently R_{205} or R_{210} ;

wherein each heterocycloalkyl group at each occurrence is optionally substituted with 1, 2, or 3 groups that are independently R_{210} ;

wherein each heteroaryl group at each occurrence is optionally substituted with 1, 2, or 3 groups that are independently R_{205} , R_{210} , or C_1 - C_6 alkyl substituted with 1, 2, or 3 groups that are independently R_{205} or R_{210} ;

R_{205} at each occurrence is independently selected from the group consisting of C_1 - C_6 alkyl, halogen, -OH, -O-phenyl, -SH, -C \equiv N, -CF $_3$, C_1 - C_6 alkoxy, NH $_2$, NH(C_1 - C_6 alkyl), and N-(C_1 - C_6 alkyl)(C_1 - C_6 alkyl);

R_{210} at each occurrence is independently selected from the group consisting of C_1 - C_6 alkyl optionally substituted with 1, 2, or 3 R_{205} groups; C_2 - C_6 alkenyl optionally substituted with 1, 2, or 3 R_{205} groups; C_2 - C_6 alkynyl optionally substituted with 1, 2, or 3 R_{205} groups; halogen; C_1 - C_6 alkoxy; C_1 - C_6 haloalkoxy; -NR $_{220}$ R $_{225}$; OH; C \equiv N; C_3 - C_7 cycloalkyl optionally substituted with 1, 2, or 3 R_{205} groups; -CO-(C_1 - C_4 alkyl); -SO $_2$ -NR $_{235}$ R $_{240}$; -CO-NR $_{235}$ R $_{240}$; -SO $_2$ -(C_1 - C_4 alkyl); and =O; wherein

R_{215} at each occurrence is independently selected from the group consisting of C_1 - C_6 alkyl, -(CH $_2$) $_{0-2}$ -(aryl), C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_7 cycloalkyl, and -(CH $_2$) $_{0-2}$ -(heteroaryl), -(CH $_2$) $_{0-2}$ -(heterocycloalkyl); wherein the aryl group at each occurrence is optionally substituted with 1, 2, or 3 groups that are independently R_{205} or R_{210} ; wherein the heterocycloalkyl group at each occurrence is optionally substituted with 1, 2, or 3 R_{210} ; wherein

each heteroaryl group at each occurrence is optionally substituted with 1, 2, or 3 R₂₁₀;

R₂₂₀ and R₂₂₅ at each occurrence are independently selected from the group consisting of -H, -C₁-C₆ alkyl, hydroxy C₁-C₆ alkyl, amino C₁-C₆ alkyl; halo C₁-C₆ alkyl; -C₃-C₇ cycloalkyl, -(C₁-C₂ alkyl)-(C₃-C₇ cycloalkyl), -(C₁-C₆ alkyl)-O-(C₁-C₃ alkyl), -C₂-C₆ alkenyl, -C₂-C₆ alkynyl, -C₁-C₆ alkyl chain with one double bond and one triple bond, -aryl, -heteroaryl, and -heterocycloalkyl; wherein the aryl group at each occurrence is optionally substituted with 1, 2, or 3 R₂₇₀ groups, wherein

R₂₇₀ at each occurrence is independently R₂₀₅, C₁-C₆ alkyl optionally substituted with 1, 2, or 3 R₂₀₅ groups; C₂-C₆ alkenyl optionally substituted with 1, 2, or 3 R₂₀₅ groups; C₂-C₆ alkynyl optionally substituted with 1, 2, or 3 R₂₀₅ groups; halogen; C₁-C₆ alkoxy; C₁-C₆ haloalkoxy; NR₂₃₅R₂₄₀; OH; C≡N; C₃-C₇ cycloalkyl optionally substituted with 1, 2, or 3 R₂₀₅ groups; -CO-(C₁-C₄ alkyl); -SO₂-NR₂₃₅R₂₄₀; -CO-NR₂₃₅R₂₄₀; -SO₂-(C₁-C₄ alkyl); and =O; wherein the heterocycloalkyl group at each occurrence is optionally substituted with 1, 2, or 3 R₂₀₅ groups; wherein each heteroaryl group at each occurrence is optionally substituted with 1, 2, or 3 R₂₀₅ groups;

R₂₃₅ and R₂₄₀ at each occurrence are independently H, or C₁-C₆ alkyl;

R₂₄₅ and R₂₅₀ at each occurrence are independently selected from the group consisting of H, C₁-C₄ alkyl, C₁-C₄ hydroxyalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, -(CH₂)₀₋₄-C₃-C₇ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, aryl C₁-C₄ alkyl, heteroaryl C₁-C₄ alkyl, and phenyl; or

R₂₄₅ and R₂₅₀ are taken together with the carbon to which they are attached to form a carbocycle of 3, 4, 5, 6, or 7 carbon atoms, optionally where one carbon atom is replaced by a heteroatom selected from the group consisting of -O-, -S-, -SO₂-, and -NR₂₂₀-;

R_{255} and R_{260} at each occurrence are independently selected from the group consisting of H; C_1-C_6 alkyl optionally substituted with 1, 2, or 3 R_{205} groups; C_2-C_6 alkenyl optionally substituted with 1, 2, or 3 R_{205} groups; C_2-C_6 alkynyl optionally substituted with 1, 2, or 3 R_{205} groups; $-(CH_2)_{1-2}-S(O)_{0-2}-(C_1-C_6 \text{ alkyl})$; $-(CH_2)_{0-4}-C_3-C_7$ cycloalkyl optionally substituted with 1, 2, or 3 R_{205} groups; $-(C_1-C_4 \text{ alkyl})$ -aryl; $-(C_1-C_4 \text{ alkyl})$ -heteroaryl; $-(C_1-C_4 \text{ alkyl})$ -heterocycloalkyl; -aryl; -heteroaryl; -heterocycloalkyl; $-(CH_2)_{1-4}-R_{265}$ - $(CH_2)_{0-4}$ -aryl; $-(CH_2)_{1-4}-R_{265}-(CH_2)_{0-4}$ -heteroaryl; and; $-(CH_2)_{1-4}-R_{265}-(CH_2)_{0-4}$ -heterocycloalkyl; wherein R_{265} at each occurrence is independently -O-, -S- or -N(C_1-C_6 alkyl)-; each aryl or phenyl is optionally substituted with 1, 2, or 3 groups that are independently R_{205} , R_{210} , or C_1-C_6 alkyl substituted with 1, 2, or 3 groups that are independently R_{205} or R_{210} ; each heteroaryl is optionally substituted with 1, 2, 3, or 4 R_{200} , each heterocycloalkyl is optionally substituted with 1, 2, 3, or 4 R_{210} .

2. A compound according to claim 1 wherein R_1 is $(CH_2)_{n_1}-(R_{1-aryl})$ where n_1 is zero or one and R_{1-aryl} is phenyl optionally substituted with 1, 2, 3, or 4 groups independently selected from C_1-C_6 alkyl optionally substituted with 1, 2, or 3 substituents selected from the group consisting of C_1-C_3 alkyl, halogen, -OH, -SH, $-NR_{1-a}R_{1-b}$, $-C\equiv N$, $-CF_3$, and C_1-C_3 alkoxy; halogen; C_1-C_6 alkoxy; $-NR_{N-2}R_{N-3}$; and OH; wherein R_{N-2} and R_{N-3} at each occurrence are independently selected from the group consisting of $-C_1-C_8$ alkyl optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of -OH, $-NH_2$,

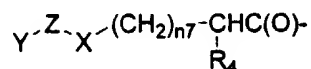
phenyl and halogen; -C₃-C₈ cycloalkyl; -(C₁-C₂ alkyl)-
(C₃-C₈ cycloalkyl); -(C₁-C₆ alkyl)-O-(C₁-C₃ alkyl); -
C₂-C₆ alkenyl; -C₂-C₆ alkynyl; -C₁-C₆ alkyl chain with
one double bond and one triple bond; aryl;
heteroaryl; heterocycloalkyl;

or

R_{N-2}, R_{N-3} and the nitrogen to which they are attached form
a 5, 6, or 7 membered heterocycloalkyl or heteroaryl
group, wherein said heterocycloalkyl or heteroaryl
group is optionally fused to a benzene, pyridine, or
pyrimidine ring, and said groups are unsubstituted or
substituted with 1, 2, 3, 4, or 5 groups that at each
occurrence are independently C₁-C₆ alkyl, C₁-C₆
alkoxy, halogen, halo C₁-C₆ alkyl, halo C₁-C₆ alkoxy,
-CN, -NO₂, -NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)(C₁-C₆
alkyl), -OH, -C(O)NH₂, -C(O)NH(C₁-C₆ alkyl),
-C(O)N(C₁-C₆ alkyl)(C₁-C₆ alkyl), C₁-C₆ alkoxy C₁-C₆
alkyl, C₁-C₆ thioalkoxy, and C₁-C₆ thioalkoxy C₁-C₆
alkyl.

3. A compound according to claim 2, wherein

R_N is:



wherein

R₄ is NH₂; -NH-(CH₂)_{n₆}-R₄₋₁; -NHR₈; -NR₅₀C(O)R₅; or -NR₅₀CO₂R₅₁;

wherein

n₆ is 0, 1, 2, or 3;

n₇ is 0, 1, 2, or 3;

R₄₋₁ is selected from the group consisting of -SO₂-(C₁-C₈
alkyl), -SO-(C₁-C₈ alkyl), -S-(C₁-C₈ alkyl), -S-CO-
(C₁-C₆ alkyl), -SO₂-NR₄₋₂R₄₋₃; -CO-C₁-C₂ alkyl; -CO-NR₄₋₃
R₄₋₄;

R₄₋₂ and R₄₋₃ are independently H, C₁-C₃ alkyl, or C₃-C₆ cycloalkyl;

R₄₋₄ is alkyl, phenylalkyl, C₂-C₄ alkanoyl, or phenylalkanoyl;

5 R₅ is selected from the group consisting of cyclopropyl, cyclopentyl, and cyclohexyl; C₁-C₆ alkyl optionally substituted with 1, 2, or 3 groups that are independently halogen, -NR₆R₇, C₁-C₄ alkoxy, C₅-C₆ heterocycloalkyl, C₅-C₆ heteroaryl, phenyl, C₃-C₇ cycloalkyl, -S-C₁-C₄ alkyl, -SO₂-C₁-C₄ alkyl, -CO₂H, 10 -CONR₆R₇, -CO₂-C₁-C₄ alkyl, or phenyloxy; heteroaryl optionally substituted with 1, 2, or 3 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, C₁-C₄ haloalkyl, or OH; heterocycloalkyl optionally substituted with 1, 2, or 3 groups that are 15 independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, or C₂-C₄ alkanoyl; phenyl optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, OH, C₁-C₄ alkyl, C₁-C₄ alkoxy, or C₁-C₄ haloalkyl; and 20 -NR₆R₇; wherein

R₆ and R₇ are independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkanoyl, phenyl, -SO₂-C₁-C₄ alkyl, and phenyl C₁-C₄ alkyl;

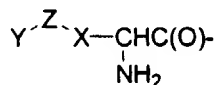
R₈ is selected from the group consisting of -SO₂- 25 heteroaryl optionally substituted with 1 or 2 groups that are independently C₁-C₄ alkyl or halogen; -SO₂-aryl, -SO₂-heterocycloalkyl, -C(O)NHR₉, heterocycloalkyl, -S-C₂-C₄ alkanoyl, wherein R₉ is phenyl C₁-C₄ alkyl, C₁-C₆ alkyl, or H;

30 R₅₀ is H or C₁-C₆ alkyl;

R₅₁ is selected from the group consisting of phenyl C₁-C₄ alkyl; C₁-C₆ alkyl optionally substituted with 1, 2, or 3 groups that are independently halogen, cyano, -NR₆R₇, -C(O)NR₆R₇, C₃-C₇ or -C₁-C₄ alkoxy;

heterocycloalkyl optionally substituted with 1 or 2 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, C₂-C₄ alkanoyl, phenyl C₁-C₄ alkyl, and -SO₂ C₁-C₄ alkyl; heterocycloalkylalkyl optionally substituted with 1 or 2 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, C₂-C₄ alkanoyl, phenyl C₁-C₄ alkyl, and -SO₂ C₁-C₄ alkyl; alkenyl; alkynyl; heteroaryl optionally substituted with 1, 2, or 3 groups that are independently OH, C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, NH₂, NH(C₁-C₆ alkyl) or N(C₁-C₆ alkyl)(C₁-C₆ alkyl); heteroarylalkyl optionally substituted with 1, 2, or 3 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, NH₂, NH(C₁-C₆ alkyl) or N(C₁-C₆ alkyl)(C₁-C₆ alkyl); phenyl; C₃-C₈ cycloalkyl, and cycloalkylalkyl, wherein the phenyl; C₃-C₈ cycloalkyl, and cycloalkylalkyl groups are optionally substituted with 1, 2, 3, 4 or 5 groups that are independently halogen, CN, NO₂, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₂-C₆ alkanoyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, hydroxy, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy C₁-C₆ alkyl, C₁-C₆ thioalkoxy, C₁-C₆ thioalkoxy C₁-C₆ alkyl, or C₁-C₆ alkoxy C₁-C₆ alkoxy.

4. A compound according to claim 3, wherein



X is C₁-C₄ alkylidenyl optionally optionally substituted with 1, 2, or 3 methyl groups; or -NR₄₋₆-; or

R₄ and R₄₋₆ combine to form -(CH₂)_{n10}-, wherein n₁₀ is 1, 2, 3, or 4;

Z is selected from a bond; SO₂; SO; S; and C(O);

Y is selected from H; C₁-C₄ haloalkyl; C₅-C₆ heterocycloalkyl containing at least one N, O, or S; phenyl; OH; -N(Y₁)(Y₂); C₁-C₁₀ alkyl optionally substituted with 1 thru

3 substituents which can be the same or different and are selected from halogen, hydroxy, alkoxy, thioalkoxy, and haloalkoxy; C₃-C₈ cycloalkyl optionally substituted with 1, 2, or 3 groups independently selected from C₁-C₃ alkyl, and halogen; alkoxy; phenyl optionally substituted with halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, CN or NO₂; phenyl C₁-C₄ alkyl optionally substituted with halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, CN or NO₂; wherein

Y₁ and Y₂ are the same or different and are H; C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 substituents selected from the group consisting of halogen, C₁-C₄ alkoxy, C₃-C₈ cycloalkyl, and OH; C₂-C₆ alkenyl; C₂-C₆ alkanoyl; phenyl; -SO₂-C₁-C₄ alkyl; phenyl C₁-C₄ alkyl; and C₃-C₈ cycloalkyl C₁-C₄ alkyl; or

-N(Y₁)(Y₂) forms a ring selected from piperazinyl, piperidinyl, morpholinyl, and pyrrolidinyl, wherein each ring is optionally substituted with 1, 2, 3, or 4 groups that are independently C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkoxy C₁-C₆ alkyl, or halogen;

R₂₀ at each occurrence is independently selected from hydrogen, C₁-C₆ alkyl, C₁-C₆ alkoxy C₁-C₆ alkyl, halo C₁-C₆ alkyl, C₁-C₆ alkanoyl, each of which is unsubstituted or substituted with 1, or 2 groups independently selected from halogen, C₁-C₆ alkyl, hydroxy, C₁-C₆ alkoxy, NH₂, and -R₂₆-R₂₇,

wherein

R₂₆ is selected from -C(O)-, -SO₂-, -CO₂-, -C(O)NH-, and -C(O)N(C₁-C₆ alkyl)-;

R₂₇ is selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, aryl C₁-C₆ alkyl, heterocycloalkyl, and heteroaryl, wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, halo C₁-C₆ alkyl, hydroxy C₁-C₆ alkyl, -C(O)NH₂, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆

alkyl)(C₁-C₆ alkyl), -C(O)NH(C₁-C₆ alkyl), or -
C(O)N(C₁-C₆ alkyl)(C₁-C₆ alkyl).

5. A compound according to claim 4, wherein

- 5 R₁ is benzyl which is optionally substituted with 1, 2, 3, or 4 groups independently selected from halogen, C₁-C₄ alkoxy, hydroxy, and C₁-C₄ alkyl optionally substituted with 1, 2, or 3 substituents halogen, OH, SH, NH₂, NH(C₁-C₆ alkyl), N-(C₁-C₆ alkyl)(C₁-C₆ alkyl), C≡N, CF₃;
- 10 R₂ and R₃ are independently selected from H or C₁-C₄ alkyl optionally substituted with 1 substituent selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, NH₂, NH(C₁-C₆ alkyl), and NH(C₁-C₆ alkyl)(C₁-C₆ alkyl);
- R₂₀ at each occurrence is independently hydrogen, C₁-C₆ alkyl, 15 C₁-C₂ alkoxy C₁-C₄ alkyl, halo C₁-C₄ alkyl, C₂-C₆ alkanoyl, each of which is unsubstituted or substituted with 1 or 2 groups independently selected from halogen, hydroxy, and NH₂;
- R_C is C₁-C₈ alkyl optionally substituted with 1, 2, or 3 groups 20 independently selected from R₂₀₅, -SH, -C=ONR₂₃₅R₂₄₀, and -S(=O)₂NR₂₃₅R₂₄₀; -(CH₂)₀₋₃-(C₃-C₆) cycloalkyl wherein the cycloalkyl is optionally substituted with 1, 2, or 3 groups independently selected from R₂₀₅, -CO₂H, and -CO₂-(C₁-C₄ alkyl); -(CR₂₄₅R₂₅₀)₀₋₄-phenyl optionally substituted 25 with 1, 2, or 3 R₂₀₀; -(CR₂₄₅R₂₅₀)₀₋₃-pyridyl; -(CR₂₄₅R₂₅₀)₀₋₃-pyridazinyl; -(CR₂₄₅R₂₅₀)₀₋₃-pyrimidinyl; -(CR₂₄₅R₂₅₀)₀₋₃-pyrazinyl; -(CR₂₄₅R₂₅₀)₀₋₃-furyl; -(CR₂₄₅R₂₅₀)₀₋₃-indolyl; -(CR₂₄₅R₂₅₀)₀₋₃-thienyl; -(CR₂₄₅R₂₅₀)₀₋₃-pyrrolyl; -(CR₂₄₅R₂₅₀)₀₋₃-pyrazolyl; (CR₂₄₅R₂₅₀)₀₋₃-benzoxazolyl; -(CR₂₄₅R₂₅₀)₀₋₃- 30 imidazolyl; each of the above heteroaryl groups is optionally substituted with 1, 2, 3, or 4 R₂₀₀; -(CR₂₄₅R₂₅₀)₀₋₃-imidazolidinyl; (CR₂₄₅R₂₅₀)₀₋₃-tetrahydrofuryl; (CR₂₄₅R₂₅₀)₀₋₃-tetrahydropyranyl; (CR₂₄₅R₂₅₀)₀₋₃-piperazinyl; (CR₂₄₅R₂₅₀)₀₋₃-pyrrolidinyl; (CR₂₄₅R₂₅₀)₀₋₃-piperidinyl; (CR₂₄₅R₂₅₀)₀₋₃-

indoliny1; each of the above heterocycloalkyl groups is optionally substituted with 1, 2, 3, or 4 R_{210} ; $(CH_2)_{0-1}-CH((CH_2)_{0-4}-OH)-(CH_2)_{0-1}-phenyl$; $-(CH_2)_{0-1}-CH(C_1-C_4 hydroxyalkyl)-(CH_2)_{0-1}-pyridyl$;

5 R_{200} at each occurrence is independently C_1-C_6 alkyl optionally substituted with 1, 2, or 3 R_{205} groups; OH ; $-NO_2$; halogen; $-CO_2H$; $C\equiv N$; $-(CH_2)_{0-4}-CO-NR_{220}R_{225}$; $-(CH_2)_{0-4}-CO-(C_1-C_8 alkyl)$; $-(CH_2)_{0-4}-CO_2R_{215}$; and $-(CH_2)_{0-4}-O-(C_1-C_6 alkyl$ optionally substituted with 1,
10 2, 3, or 5 $-F$);

R_{205} at each occurrence is independently C_1-C_6 alkyl, halogen, $-OH$, $-O-phenyl$, $-SH$, $-C\equiv N$, $-CF_3$, C_1-C_6 alkoxy, NH_2 , $NH(C_1-C_6 alkyl)$, and $N-(C_1-C_6 alkyl)(C_1-C_6 alkyl)$;

15 R_{210} at each occurrence is independently C_1-C_6 alkyl optionally substituted with 1 or 2 R_{205} groups; halogen; C_1-C_4 alkoxy; C_1-C_4 haloalkoxy; $-NR_{220}R_{225}$; OH ; $C\equiv N$; C_3-C_7 cycloalkyl optionally substituted with 1 or 2 R_{205} groups; $-CO-(C_1-C_4 alkyl)$; $-SO_2-NR_{235}R_{240}$; $-CO-NR_{235}R_{240}$; $-SO_2-(C_1-C_4 alkyl)$; and $=O$; wherein
20

R_{215} at each occurrence is independently C_1-C_6 alkyl, $-(CH_2)_{0-2}-(phenyl)$, C_3-C_6 cycloalkyl, $-(CH_2)_{0-2}-(pyridyl)$, $-(CH_2)_{0-2}-(pyrrolyl)$, $-(CH_2)_{0-2}-(imidazolyl)$, $-(CH_2)_{0-2}-(pyrimidyl)$, $-(CH_2)_{0-2}-(pyrrolidinyl)$, $-(CH_2)_{0-2}-(imidazolidinyl)$, $-(CH_2)_{0-2}-(piperazinyl)$, $-(CH_2)_{0-2}-(piperidinyl)$, and $-(CH_2)_{0-2}-(morpholinyl)$; wherein the phenyl group at each occurrence is optionally substituted with 1 or 2 groups that are independently R_{205} or R_{210} ; wherein
25 each heterocycloalkyl group at each occurrence is optionally substituted with 1 or 2 R_{210} ; wherein each heteroaryl group at each occurrence is optionally substituted with 1 or 2 R_{210} ;
30

R₂₂₀ and R₂₂₅ at each occurrence are independently -H, -C₁-C₄ alkyl, hydroxy C₁-C₄ alkyl, halo C₁-C₄ alkyl; -C₃-C₆ cycloalkyl, and -(C₁-C₄ alkyl)-O-(C₁-C₂ alkyl);

5 R₂₃₅ and R₂₄₀ at each occurrence are independently H, or C₁-C₆ alkyl;

R₂₄₅ and R₂₅₀ at each occurrence are independently H, C₁-C₄ alkyl, C₁-C₄ hydroxyalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, or

10 R₂₄₅ and R₂₅₀ are taken together with the carbon to which they are attached to form a carbocycle of 3, 5, or 6 carbon atoms.

6. A compound according to claim 5, wherein
15 X is-C₁-C₃ alkylidenyl optionally optionally substituted with 1 methyl group;

Z is SO₂; SO; S; or C(O);

20 Y is OH; -N(Y₁)(Y₂); phenyl; benzyl; or C₁-C₁₀ alkyl optionally substituted with 1 or 2 substituents which can be the same or different and are selected from halogen, hydroxy, methoxy, ethoxy, thiomethoxy, thioethoxy, and CF₃; wherein Y₁ and Y₂ are the same or different and are H; C₁-C₄ alkyl optionally substituted with 1 or 2 substituents selected from halogen, methoxy, ethoxy, cyclopropyl, and OH; or

25 -N(Y₁)(Y₂) forms a ring selected from piperazinyl, piperidinyl, morpholinyl, and pyrrolidinyl, wherein each ring is optionally substituted with 1 or 2 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, or halogen;

30 R₁ is benzyl which is optionally substituted with 1, 2, or 3 groups independently selected from methyl, ethyl, n-propyl, isopropyl, hydroxymethyl, monohalomethyl, dihalomethyl, trihalomethyl, -CH₂CF₃, methoxymethyl,

halogen, methoxy, ethoxy, n-propyloxy, isopropyloxy, and OH;

R₂ and R₃ are independently H or C₁-C₄ alkyl;

R₂₀ at each occurrence is independently hydrogen, C₁-C₄ alkyl,

5 or C₂-C₄ alkanoyl;

R_C is C₁-C₆ alkyl optionally substituted with 1, 2, or 3 R₂₀₅

groups; cyclopropyl, cyclopropylmethyl, cyclopentyl,

cyclopentylmethyl, cyclohexyl, cyclohexylmethyl;

10 -(CR₂₄₅R₂₅₀)₀₋₃-phenyl optionally substituted with 1 or 2 R₂₀₀ groups; -(CR₂₄₅R₂₅₀)₀₋₃-pyridyl optionally substituted with 1

or 2 R₂₀₀; -(CR₂₄₅R₂₅₀)₀₋₃-piperazinyl; or (CR₂₄₅R₂₅₀)₀₋₃-

pyrrolidinyl; -(CR₂₄₅R₂₅₀)₀₋₃-piperidinyl; each of the above

heterocycloalkyl groups is optionally substituted with 1

or 2 R₂₁₀ groups;

15 R₂₀₀ at each occurrence is independently selected from C₁-

C₄ alkyl optionally substituted with 1 or 2 R₂₀₅ groups; OH; and halogen;

R₂₀₅ at each occurrence is independently selected from C₁-

20 C₄ alkyl, halogen, -OH, -SH, -C≡N, -CF₃, and C₁-C₄ alkoxy;

R₂₁₀ at each occurrence is independently selected from C₁-

C₄ alkyl optionally substituted with 1 or 2 R₂₀₅

groups; halogen; C₁-C₄ alkoxy; OCF₃; NH₂, NH(C₁-C₆

alkyl); N(C₁-C₆ alkyl)(C₁-C₆ alkyl); OH; and -CO-(C₁-C₄

25 alkyl); wherein

R₂₄₅ and R₂₅₀ at each occurrence are independently selected from H, C₁-C₄ hydroxyalkyl, C₁-C₄ alkoxy, or

R₂₄₅ and R₂₅₀ are taken together with the carbon to which they are attached to form a carbocycle of 3, 5, or 6 carbon atoms.

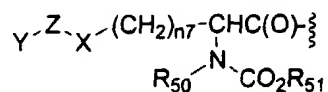
30

7. A compound according to claim 4 that is selected from

S-butyl-N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-D-cysteinamide;

(2R)-2-amino-N-((1S,2R)-1-benzyl-2-hydroxy-3-((3-methoxybenzyl)amino)propyl)-5-oxo-5-piperidin-1-ylpentanamide.

R_N is:



R₅₀ is H or C₁-C₆ alkyl;

R₅₁ is phenyl C₁-C₄ alkyl; C₁-C₆ alkyl optionally substituted with 1, 2, or 3 groups that are independently halogen, cyano, -NR₆R₇, -C(O)NR₆R₇, or -C₁-C₄ alkoxy; heterocycloalkyl optionally substituted with 1 or 2 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, C₂-C₄ alkanoyl, phenyl C₁-C₄ alkyl, and -SO₂ C₁-C₄ alkyl; heterocycloalkylalkyl optionally substituted with 1 or 2 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, C₂-C₄ alkanoyl, phenyl C₁-C₄ alkyl, and -SO₂ C₁-C₄ alkyl; alkenyl; alkynyl; heteroaryl optionally substituted with 1, 2, or 3 groups that are independently OH, C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, NH₂, NH(C₁-C₆ alkyl) or N(C₁-C₆ alkyl)(C₁-C₆ alkyl); heteroarylalkyl optionally substituted with 1, 2, or 3 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, NH₂, NH(C₁-C₆ alkyl) or N(C₁-C₆ alkyl)(C₁-C₆ alkyl); phenyl; C₃-C₈ cycloalkyl; or cycloalkylalkyl; wherein the phenyl, C₃-C₈ cycloalkyl, and cycloalkylalkyl groups are optionally substituted with 1, 2, 3, 4 or 5 groups that are independently halogen, CN, NO₂, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₂-C₆ alkanoyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, hydroxy, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy C₁-C₆ alkyl, C₁-C₆ thioalkoxy, C₁-C₆ thioalkoxy C₁-C₆ alkyl, or C₁-C₆ alkoxy C₁-C₆ alkoxy;

R₆ and R₇ are independently H, C₁-C₆ alkyl, C₂-C₆

alkanoyl, phenyl, -SO₂-C₁-C₄ alkyl, or phenyl C₁-C₄ alkyl;

X is C₁-C₄ alkylidenyl optionally optionally substituted with 1, 2, or 3 methyl groups; or -NR₄₋₆-; or

R₄ and R₄₋₆ combine to form -(CH₂)_{n10}-, wherein

n₁₀ is 1, 2, 3, or 4;

Z is a bond; SO₂; SO; S; or C(O);

Y is H; C₁-C₄ haloalkyl; C₅-C₆ heterocycloalkyl containing at least one N, O, or S; phenyl; OH; -N(Y₁)(Y₂); C₁-C₁₀ alkyl optionally substituted with 1 thru 3 substituents which

- can be the same or different and are selected from halogen, hydroxy, alkoxy, thioalkoxy, and haloalkoxy; C₃-C₈ cycloalkyl optionally substituted with 1, 2, or 3 groups independently selected from C₁-C₃ alkyl, and
- 5 halogen; alkoxy; phenyl optionally substituted with halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, CN or NO₂; or phenyl C₁-C₄ alkyl optionally substituted with halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, CN or NO₂; wherein
- Y₁ and Y₂ are the same or different and are H; C₁-C₁₀ alkyl
- 10 optionally substituted with 1, 2, or 3 substituents selected from halogen, C₁-C₄ alkoxy, C₃-C₈ cycloalkyl, and OH; C₂-C₆ alkenyl; C₂-C₆ alkanoyl; phenyl; -SO₂-C₁-C₄ alkyl; phenyl C₁-C₄ alkyl; or C₃-C₈ cycloalkyl C₁-C₄ alkyl; or
- 15 -N(Y₁)(Y₂) forms a ring selected from piperazinyl, piperidinyl, morpholinyl, and pyrrolidinyl, wherein each ring is optionally substituted with 1, 2, 3, or 4 groups that are independently C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkoxy C₁-C₆ alkyl, or halogen;
- 20 R₂₀ at each occurrence is independently hydrogen, C₁-C₆ alkyl, C₁-C₆ alkoxy C₁-C₆ alkyl, halo C₁-C₆ alkyl, or C₁-C₆ alkanoyl, each of which is unsubstituted or substituted with 1, or 2 groups independently selected from halogen, C₁-C₆ alkyl, hydroxy, C₁-C₆ alkoxy, NH₂, and -R₂₆-R₂₇,
- 25 wherein
- R₂₆ is -C(O)-, -SO₂-, -CO₂-, -C(O)NH-, or -C(O)N(C₁-C₆ alkyl)-;
- R₂₇ is C₁-C₆ alkyl, C₁-C₆ alkoxy, aryl C₁-C₆ alkyl, heterocycloalkyl, or heteroaryl, wherein each of the
- 30 above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, halo C₁-C₆ alkyl, hydroxy C₁-C₆ alkyl, -C(O)NH₂, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆

alkyl)(C₁-C₆ alkyl), -C(O)NH(C₁-C₆ alkyl), or -
C(O)N(C₁-C₆ alkyl)(C₁-C₆ alkyl).

9. A compound according to claim 8, wherein

5 X is-C₁-C₃ alkylidenyl;

Z is SO₂; SO; S; or C(O);

Y is OH; -N(Y₁)(Y₂); phenyl; benzyl; or C₁-C₁₀ alkyl optionally
substituted with 1 or 2 substituents which can be the same
or different and are selected from halogen, hydroxy,
10 methoxy, ethoxy, thiomethoxy, thioethoxy, and CF₃; wherein
Y₁ and Y₂ are the same or different and are H; C₁-C₄ alkyl
optionally substituted with 1 or 2 substituents
selected from halogen, methoxy, ethoxy, cyclopropyl,
and OH; or

15 -N(Y₁)(Y₂) forms a ring selected from piperazinyl,
piperidinyl, morpholinyl, and pyrrolidinyl, wherein
each ring is optionally substituted with 1 or 2
groups that are independently C₁-C₄ alkyl, C₁-C₄
alkoxy, or halogen;

20 R₁ is benzyl which is optionally substituted with 1, 2, or 3
groups independently selected from methyl, ethyl, n-
propyl, isopropyl, hydroxymethyl, monohalomethyl,
dihalomethyl, trihalomethyl, -CH₂CF₃, methoxymethyl,
halogen, methoxy, ethoxy, n-propyloxy, isopropyloxy, and
25 OH;

R₂ and R₃ are independently H or C₁-C₄ alkyl,

R₂₀ at each occurrence is independently hydrogen, C₁-C₄ alkyl,
or C₂-C₄ alkanoyl;

R_C is C₁-C₆ alkyl optionally substituted with 1, 2, or 3 R₂₀₅
30 groups; cyclopropyl, cyclopropylmethyl, cyclopentyl,
cyclopentylmethyl, cyclohexyl, cyclohexylmethyl;
-(CR₂₄₅R₂₅₀)₀₋₃-phenyl optionally substituted with 1 or 2 R₂₀₀
groups; or -(CR₂₄₅R₂₅₀)₀₋₃-pyridyl optionally substituted
with 1 or 2 R₂₀₀;

R₂₀₀ at each occurrence is independently C₁-C₄ alkyl optionally substituted with 1 or 2 R₂₀₅ groups; OH; or halogen;

5 R₂₀₅ at each occurrence is independently C₁-C₄ alkyl, halogen, -OH, -SH, -C≡N, -CF₃, or C₁-C₄ alkoxy;

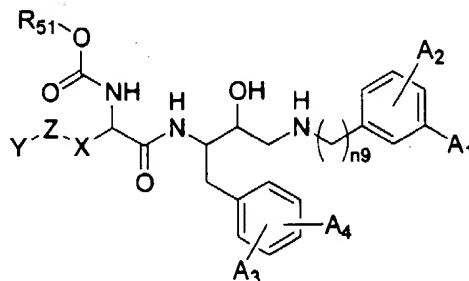
R₂₄₅ and R₂₅₀ at each occurrence are independently H, C₁-C₄ hydroxyalkyl, or C₁-C₄ alkoxy, or

10 R₂₄₅ and R₂₅₀ are taken together with the carbon to which they are attached to form a carbocycle of 3 carbon atoms.

10. A compound according to claim 9, wherein
R₅₁ is benzyl; phenethyl; C₁-C₆ alkyl optionally substituted
with 1, 2, or 3 groups that are independently halogen,
15 cyano, -NR₆R₇, -C(O)NR₆R₇, or -C₁-C₄ alkoxy; pyrrolidinyl, tetrahydrofuryl, tetrahydro-thienyl 1,1-dioxide, tetrahydrothienyl, pyranyl, piperidinyl, pyrrolidinonyl, each of which is optionally substituted with 1 or 2 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen,
20 C₂-C₄ alkanoyl, benzyl, and -SO₂ C₁-C₄ alkyl; pyrrolidinonyl C₁-C₄ alkyl optionally substituted with 1 or 2 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, C₂-C₄ alkanoyl, C₁-C₄ alkyl, and -SO₂ C₁-C₄ alkyl; C₂-C₄ alkenyl; C₂-C₄ alkynyl; pyridinyl C₁-C₄ alkyl
25 optionally substituted with 1, or 2 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, NH₂, NH(C₁-C₆ alkyl) or N(C₁-C₆ alkyl)(C₁-C₆ alkyl); cyclopentyl; cyclohexyl; or cyclopropylmethyl; wherein the cycloalkyl, and cycloalkylalkyl groups are optionally substituted with
30 1, or 2 groups that are independently halogen, CN, NO₂, methyl, ethyl, methoxy, ethoxy, C₂-C₄ alkanoyl, CF₃, OCF₃, or hydroxy;
R₆ and R₇ are independently H, C₁-C₄ alkyl, C₂-C₄ alkanoyl, or benzyl;

Y is OH; -N(Y₁)(Y₂); phenyl; benzyl; or C₁-C₁₀ alkyl optionally substituted with 1 or 2 substituents which can be the same or different and are selected from halogen, hydroxy, methoxy, ethoxy, thiomethoxy, thioethoxy, and CF₃; wherein
 5 Y₁ and Y₂ are the same or different and are H or C₁-C₄ alkyl optionally substituted with 1 or 2 substituents selected from halogen, methoxy, ethoxy, cyclopropyl, and OH.

10 11. A compound according to claim 10 of the formula



wherein

n₉ is 1 or 2;

A₁ and A₂ are independently H, methyl, ethyl, propyl, methoxy,

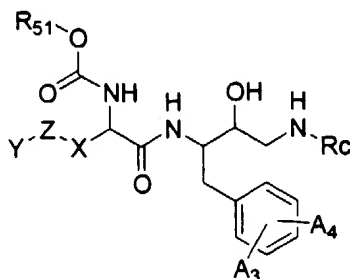
15 F, Cl, Br, I, or CF₃; or

A₃ and A₄ are independently F, Cl, Br, I, methyl, methoxy, or H.

12. A compound according to claim 8, wherein

20 R_C is C₃-C₈ alkyl, cyclopropyl, cyclopentyl, cyclohexyl, or - (C₁-C₄)alkyl-cyclopropyl.

13. A compound according to claim 12 of the formula



wherein

A₃ and A₄ are independently F, Cl, Br, I, methyl, ethyl, methoxy, ethoxy, or H;

X is C₁ or C₂ alkylidenyl;

5 Z is SO₂; SO; S; or C(O); and

Y is phenyl, C₁-C₁₀ alkyl,; or

Y is -N(Y₁)(Y₂); wherein

Y₁ and Y₂ are the same or different and are H or C₁-C₄ alkyl.

10

14. A compound according to claim 8 that is selected from

3-(butylsulfinyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(methoxy)carbonyl]-D-alaninamide;

S-butyl-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(methoxy)carbonyl]-D-cysteinamide;

N~2~-[(benzyloxy)carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(4,4,4-trifluorobutyl)sulfonyl]-D-alaninamide;

N~2~-[(benzyloxy)carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(4,4,4-trifluorobutyl)sulfinyl]-D-alaninamide;

N~2~-[(benzyloxy)carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-S-(4,4,4-trifluorobutyl)-D-cysteinamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(methoxy)carbonyl]-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(2,2,2-trifluoroethoxy)carbonyl]-D-alaninamide;

N~2~-[(2-cyanoethoxy)carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-

(butylsulfonyl)-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-
3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-{[(3R)-
pyrrolidin-3-yl]carbonyl}-D,L-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-
3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-{[(3S)-
tetrahydrofuran-3-yloxy]carbonyl}-D-alaninamide;

N~2~-{[2-(acetylamino)ethoxy]carbonyl}-3-
(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-
ethylbenzyl)amino]-2-hydroxypropyl}-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-
3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-{[(pyridin-3-
yl)methyl]oxy]carbonyl}-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-
3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-{[(pyridin-4-
yl)methyl]oxy]carbonyl}-D-alaninamide;

3-(butylsulfonyl)-N~2~-[(methoxy)carbonyl]-N~1~-
{(1S,2R)-1-(3,5-difluorobenzyl)-3-(cyclopropylamino)-2-
hydroxypropyl}-D-alaninamide;

3-(butylsulfonyl)-N~2~-[(2-cyanoethoxy)carbonyl]-N~1~-
{(1S,2R)-1-(3,5-difluorobenzyl)-3-(cyclopropylamino)-2-
hydroxypropyl}-D-alaninamide;

N~2~-[(benzyloxy)carbonyl]-3-(butylsulfonyl)-N~1~-
{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-methylbutyl)amino]-2-
hydroxypropyl}-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-
3-[(3-methylbutyl)amino]-2-hydroxypropyl}-N~2~-
[(methyloxy)carbonyl]-D-alaninamide;

N~2~-[(2-cyanoethoxy)carbonyl]-N~1~-{(1S,2R)-1-(3,5-
difluorobenzyl)-3-(cyclopropylamino)-2-hydroxypropyl}-3-[(1-
propylbutyl)sulfonyl]-D-alaninamide;

N~2~-{[2-(acetylamino)ethoxy]carbonyl}-N~1~-{(1S,2R)-1-
(3,5-difluorobenzyl)-3-(cyclopropylamino)-2-hydroxypropyl}-3-
[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-methylbutyl)amino]-2-hydroxypropyl}-N~2~-[(methoxy)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~2~-[(benzyloxy)carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-methylbutyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~2~-[[2-(diethylamino)-2-oxoethoxy]carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(methoxy)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(isopropoxy)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~2~-[(cyclopropylmethoxy)carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~2~-[(allyloxy)carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~2~-[(2-cyanoethoxy)carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~2~-[[2-(acetylamino)ethoxy]carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-N~2~-[[[(pyridin-3-yl)methyl]oxy]carbonyl]-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-

ethylbenzyl) amino]-2-hydroxypropyl)-3-[(1-propylbutyl) sulfonyl]-N~2~-{[(pyridin-4-yl)methyl]oxy]carbonyl}-D-alaninamide;

benzyl (1R)-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl) amino] carbonyl]-3-(methylsulfonyl)propylcarbamate;

N~2~-[(benzyloxy) carbonyl]-3-(butylsulfonyl)-N~1~-{[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl]-D-alaninamide trifluoroacetate;

N~2~-[(benzyloxy) carbonyl]-3-(butylsulfonyl)-N~1~-{[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl]-L-alaninamide trifluoroacetate;

N~2~-[(benzyloxy) carbonyl]-N~1~-{(1S,2S)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1R)-2-hydroxy-1-phenylethyl] amino}propyl)-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~2~-[(benzyloxy) carbonyl]-N~1~-{(1S,2S)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1R)-2-methoxy-1-phenylethyl] amino}propyl)-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~2~-[(benzyloxy) carbonyl]-N~1~-{(1S,2S)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1S)-2-methoxy-1-phenylethyl] amino}propyl)-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~2~-[(benzyloxy) carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethylphenyl) cyclopropyl] amino]-2-hydroxypropyl)-3-[(1-propylbutyl) sulfonyl]-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl)-3-[(1-propylbutyl) sulfonyl]-N~2~-{[(prop-2-ynyl) oxy]carbonyl}-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl)-N~2~-(2-methoxyethylcarbonyl)-3-[(1-propylbutyl) sulfonyl]-D-

alaninamide;

N-2--{[(3R)-1-acetylpyrrolidin-3-yl]carbonyl}-N-1--
{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-
hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-
ethylbenzyl)amino]-2-hydroxypropyl}-N-2--{[(3S)-
tetrahydrofuran-3-yloxy]carbonyl}-3-[(1-
propylbutyl)sulfonyl]-D-alaninamide;

N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-
ethylbenzyl)amino]-2-hydroxypropyl}-N-2--{[(3S)-
tetrahydrofuran-3-yloxy]carbonyl}-3-[(1-
propylbutyl)sulfonyl]-L-alaninamide;

N-2--[(benzyloxy)carbonyl]-N-1--{(1S,2R)-1-(3,5-
difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-
[(1-propylbutyl)sulfonyl]-D-alaninamide;

N-2--[(benzyloxy)carbonyl]-N-1--{(1S,2R)-1-(3,5-
difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-
[(1-propylbutyl)sulfonyl]-L-alaninamide;

N-2--[(benzyloxy)carbonyl]-N-1--{(1S,2R)-1-(3,5-
difluorobenzyl)-3-[[1-(3-ethylphenyl)cyclopropyl]amino]-2-
hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N-2--[(benzyloxy)carbonyl]-N-1--{(1S,2R)-1-(3,5-
difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-
[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N-2--[(benzyloxy)carbonyl]-N-1--{(1S,2R)-1-(3,5-
difluorobenzyl)-3-[(3-methylbutyl)amino]-2-hydroxypropyl}-3-
[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N-2--[(benzyloxy)carbonyl]-N-1--{(1S,2R)-1-(3,5-
difluorobenzyl)-3-(cyclopropylamino)-2-hydroxypropyl}-3-[(1-
propylbutyl)sulfonyl]-D,L-alaninamide;

N-2--[(benzyloxy)carbonyl]-N-1--{(1S,2R)-1-(3,5-
difluorobenzyl)-3-[(cyclopropylmethyl)amino]-2-
hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N-2--[(benzyloxy)carbonyl]-N-1--{(1S,2S)-1-(3,5-

difluorobenzyl)-3-[(3-ethylphenyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~2--[(benzyloxy)carbonyl]-N~1--[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-({2-[3-(trifluoromethyl)phenyl]ethyl}amino)propyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1--[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-3-[(1-propylbutyl)sulfonyl]-N~2--{[(pyridin-3-yl)methyl]oxy}carbonyl}-D,L-alaninamide;

N~1--[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-N~2--[(3S)-tetrahydrofuran-3-yloxy]carbonyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1--[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-N~2--[(3R)-tetrahydrofuran-3-yloxy]carbonyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1--[(1S,2R)-1-benzyl-3-[(3-methoxybenzyl)amino]-2-hydroxypropyl]-N~2--[(3S)-tetrahydrofuran-3-yloxy]carbonyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~2--[(3R)-1-acetylpyrrolidin-3-yl]carbonyl}-N~1--[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1--[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-3-[(1-propylbutyl)sulfonyl]-N~2--[(3R)-pyrrolidin-3-yl]carbonyl}-D,L-alaninamide;

N~2--[(3R)-1-benzylpyrrolidin-3-yl]carbonyl}-N~1--[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1--[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]-N~2--[(3S)-1,1-dioxidotetrahydrothien-3-yloxy]carbonyl}-3-[(1-

propylbutyl)sulfonyl]-D,L-alaninamide;

N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N-2--{[(3S)-tetrahydrothiophen-3-yloxy]carbonyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N-2--(cyclopentylcarbonyl)-N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N-2--(cyclohexylcarbonyl)-N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N-1--[(1S,2R)-3-(cyclopropylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-3-[(1-propylbutyl)sulfonyl]-N-2--{[tetrahydropyran-4-yloxy]carbonyl}-D,L-alaninamide;

N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-N-2--{[tetrahydropyran-4-yloxy]carbonyl}-D,L-alaninamide;

N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N-2--{[1-(methylsulfonyl)piperidin-4-yloxy]carbonyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N-2--{[1-acetylpiperidin-4-yloxy]carbonyl}-N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N-2--{[[[(3S)-5-oxopyrrolidin-3-yl]methyl]oxy]carbonyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N-2--{[[[(3R)-5-oxopyrrolidin-3-yl]methyl]oxy]carbonyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-

ethylbenzyl) amino]-2-hydroxypropyl)-N-2--{[2-methoxyethyl]oxy]carbonyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N-2--[(benzyloxy)carbonyl]-3-(butylsulfonyl)-N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-D,L-alaninamide;

N-1--{(1S,2R)-1-benzyl-3-[(3-methoxybenzyl)amino]-2-hydroxypropyl)-N-2--[(benzyloxy)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N-2--[(benzyloxy)carbonyl]-N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[[2-(3-methoxyphenyl)ethyl]amino]propyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N-2--[(benzyloxy)carbonyl]-N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N-5~,N-5--dipropyl-L-glutamamide; and

N-2--[(benzyloxy)carbonyl]-N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N-5~,N-5--dipropyl-D-glutamamide;

methyl (1R)-1-[[{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)amino]carbonyl]-3-oxoheptylcarbamate;

4-butyl-N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N-2--(methoxycarbonyl)-D-homoserinamide;

3-(2-butyl-1,3-dioxolan-2-yl)-N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N-2--(methoxycarbonyl)-D-alaninamide;

3-(2-butyl-1,3-dioxan-2-yl)-N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N-2--(methoxycarbonyl)-D-alaninamide;

methyl (1R)-1-[[{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)amino]carbonyl]-3,3-difluoroheptylcarbamate;

methyl (1R)-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]amino)carbonyl]-3-fluoroheptylcarbamate;

methyl (1R)-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]amino)carbonyl]-4-oxooctylcarbamate;

methyl (1R)-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]amino)carbonyl]-4-hydroxyoctylcarbamate;

methyl (1R)-3-(2-butyl-1,3-dioxolan-2-yl)-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]amino)carbonyl]propylcarbamate;

methyl (1R)-3-(2-butyl-1,3-dioxan-2-yl)-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]amino)carbonyl]propylcarbamate;

methyl (1R)-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]amino)carbonyl]-4-fluorooctylcarbamate;

methyl (1R)-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl]amino)carbonyl]-4,4-difluorooctylcarbamate;

3-(butylsulfonyl)-N-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethynylbenzyl)amino]-2-hydroxypropyl]-N-2-(methoxycarbonyl)-D-alaninamide;

3-(butylsulfonyl)-N-1-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-(trifluoromethyl)benzyl]amino)propyl]-N-2-(methoxycarbonyl)-D-alaninamide;

3-(butylsulfonyl)-N-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethylphenyl)cyclopropyl]amino]-2-hydroxypropyl]-N-2-(methoxycarbonyl)-D-alaninamide;

3-(butylsulfonyl)-N-1-[(1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethynylphenyl)cyclopropyl]amino]-2-hydroxypropyl]-N-2-(methoxycarbonyl)-D-alaninamide; and

3-(butylsulfonyl)-N-1-[(1S,2R)-1-(3,5-difluorobenzyl)-

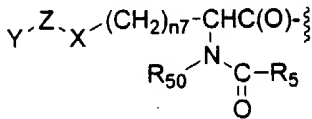
2-hydroxy-3-(1-(3-

(trifluoromethyl)phenyl]cyclopropyl)amino)propyl]-

N-2~(methoxycarbonyl)-D-alaninamide.

15. A compound according to claim 3, wherein

R_N is:



5 wherein

n_7 is 0, 1, 2, or 3;

R₅₀ is H or C₁-C₆ alkyl;

R₅ is selected from the group consisting of cyclopropyl;

cyclopentyl; cyclohexyl; C₁-C₆ alkyl optionally

substituted with 1, 2, or 3 groups that are independently halogen, $-NR_6R_7$, C_1-C_4 alkoxy, C_5-C_6 heterocycloalkyl, C_5-C_6 heteroaryl, phenyl, C_3-C_7 cycloalkyl, $-S-C_1-C_4$ alkyl, $-SO_2-C_1-C_4$ alkyl, $-CO_2H$, $-CONR_6R_7$, $-CO_2-C_1-C_4$ alkyl, or phenyloxy; heteroaryl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, C_1-C_4 haloalkyl, or OH; heterocycloalkyl optionally substituted with 1, 2, or 3 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, or C_2-C_4 alkanoyl; phenyl optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, OH, C_1-C_4 alkyl, C_1-C_4 alkoxy, or C_1-C_4 haloalkyl; and $-NR_6R_7$; wherein

R₆ and R₇ are independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkanoyl, phenyl, -SO₂-C₁-C₄ alkyl, and phenyl C₁-C₄ alkyl;

25 X is C₁-C₄ alkylidenyl optionally optionally substituted with
1, 2, or 3 methyl groups; or -NR₄₋₆-; or

R₄ and R₄₋₆ combine to form -(CH₂)_{n10}-, wherein

n_{10} is 1, 2, 3, or 4;

Z is a bond; SO₂; SO; S; or C(O);

Y is H; C₁-C₄ haloalkyl; C₅-C₆ heterocycloalkyl containing at least one N, O, or S; phenyl; OH; -N(Y₁)(Y₂); C₁-C₁₀ alkyl optionally substituted with 1 thru 3 substituents which can be the same or different and are selected from
5 halogen, hydroxy, alkoxy, thioalkoxy, and haloalkoxy; C₃-C₈ cycloalkyl optionally substituted with 1, 2, or 3 groups independently selected from C₁-C₃ alkyl, and halogen; alkoxy; phenyl optionally substituted with halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, CN or NO₂; or phenyl C₁-
10 C₄ alkyl optionally substituted with halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, CN or NO₂; wherein

Y₁ and Y₂ are the same or different and are H; C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 substituents selected from halogen, C₁-C₄ alkoxy, C₃-C₈ cycloalkyl,
15 and OH; C₂-C₆ alkenyl; C₂-C₆ alkanoyl; phenyl; -SO₂-C₁-C₄ alkyl; phenyl C₁-C₄ alkyl; or C₃-C₈ cycloalkyl C₁-C₄ alkyl; or

-N(Y₁)(Y₂) forms a ring selected from piperazinyl, piperidinyl, morpholinyl, and pyrrolidinyl, wherein
20 each ring is optionally substituted with 1, 2, 3, or 4 groups that are independently C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkoxy C₁-C₆ alkyl, or halogen; and

R₂₀ at each occurrence is independently hydrogen, C₁-C₆ alkyl, C₁-C₆ alkoxy C₁-C₆ alkyl, halo C₁-C₆ alkyl, or C₁-C₆
25 alkanoyl, each of which is unsubstituted or substituted with 1, or 2 groups independently selected from halogen, C₁-C₆ alkyl, hydroxy, C₁-C₆ alkoxy, NH₂, and -R₂₆-R₂₇,
wherein

R₂₆ is -C(O)-, -SO₂-, -CO₂-, -C(O)NH-, or -C(O)N(C₁-C₆
30 alkyl)-;

R₂₇ is C₁-C₆ alkyl, C₁-C₆ alkoxy, aryl C₁-C₆ alkyl, heterocycloalkyl, or heteroaryl, wherein each of the above is unsubstituted or substituted with 1, 2, 3,
4, or 5 groups that are independently C₁-C₄ alkyl, C₁-

C₄ alkoxy, halogen, halo C₁-C₆ alkyl, hydroxy C₁-C₆ alkyl, -C(O)NH₂, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)(C₁-C₆ alkyl), -C(O)NH(C₁-C₆ alkyl), or -C(O)N(C₁-C₆ alkyl)(C₁-C₆ alkyl).

5

16. A compound according to claim 15, wherein
R₁ is benzyl which is optionally substituted with 1, 2, 3, or 4 groups independently selected from C₁-C₄ alkyl optionally substituted with 1, or 2 substituents selected from
10 halogen, -OH, -SH, NH₂, NH(C₁-C₆ alkyl), N-(C₁-C₆ alkyl)(C₁-C₆ alkyl), -C≡N, -CF₃, and C₁-C₃ alkoxy; halogen; C₁-C₄ alkoxy; and OH.

17. A compound according to claim 16, wherein
15 X is C₁-C₃ alkylidenyl optionally optionally substituted with 1 or 2 methyl groups;
Z is SO₂; SO; S; or C(O);
Y is H; C₁-C₄ haloalkyl; pyrrolidinyl; piperidinyl;
imidazolidinyl; piperazinyl; OH; -N(Y₁)(Y₂); C₁-C₁₀ alkyl
20 optionally substituted with 1 thru 3 substituents which can be the same or different and are selected from halogen, hydroxy, C₁-C₄ alkoxy, C₁-C₄ thioalkoxy, and C₁-C₄ haloalkoxy; C₃-C₆ cycloalkyl optionally substituted with 1, 2, or 3 groups independently selected from C₁-C₃ alkyl
25 and halogen; C₁-C₄ alkoxy; phenyl, benzyl or phenethyl each of which is optionally substituted with halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, CN or NO₂; wherein
Y₁ and Y₂ are indepenently H; C₁-C₆ alkyl optionally substituted with 1, 2, or 3 substituents selected
30 from halogen, C₁-C₄ alkoxy, C₃-C₆ cycloalkyl, and OH; C₂-C₆ alkanoyl; phenyl; -SO₂-C₁-C₄ alkyl; phenyl C₁-C₄ alkyl; or C₃-C₆ cycloalkyl C₁-C₄ alkyl; or
-N(Y₁)(Y₂) forms a ring selected from piperazinyl, piperidinyl, morpholinyl, and pyrrolidinyl, wherein

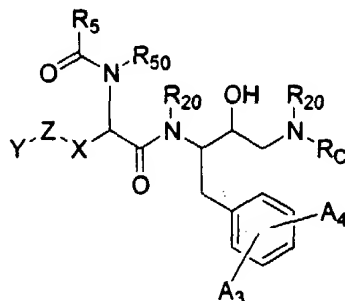
each ring is optionally substituted with 1, 2, or 3 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ alkoxy C₁-C₄ alkyl, or halogen; and R₂ and R₃ are independently H or C₁-C₄ alkyl.

5

18. A compound according to claim 17 wherein R₂₀ at each occurrence is independently H or C₁-C₄ alkyl; X is C₁ or C₂ alkylidenyl; Z is SO₂; SO; S; or C(O); and
 10 Y is phenyl; C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 halogen; or OH; or
 Y is -N(Y₁)(Y₂); wherein
 Y₁ and Y₂ are independently H or C₁-C₄ alkyl.

15

19. A compound according to claim 18, of the formula:



wherein

R_c is C₃-C₈ alkyl, cyclopropyl, cyclopentyl, cyclohexyl, or - (C₁-C₄)alkyl-cyclopropyl;

20

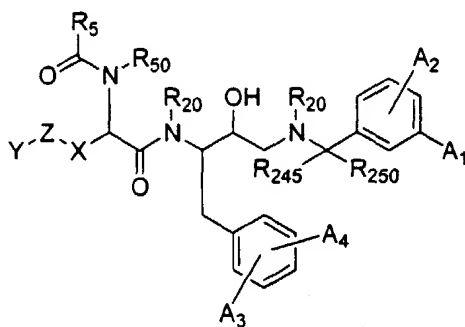
A₃ and A₄ are independently H, F, Cl, Br, or I;

R₅ is selected from cyclopropyl; cyclopentyl; cyclohexyl;

pyridyl, thiazolyl, pyrazolyl, or pyrazinyl each of which is optionally substituted with 1, 2, or 3 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, C₁-C₄ haloalkyl, or OH; piperidinyl, dihydropyridazinonyl, pyrrolidinonyl, thioxothiazolidinonyl, isoxazolyl, imidazolyl, or indolyl each of which is optionally substituted with 1, or 2 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, or C₂-C₄ alkanoyl; phenyl

25

5 20. A compound according to claim 18, wherein



pyridyl, thiazolyl, pyrazolyl, or pyrazinyl each of which is optionally substituted with 1, 2, or 3 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, C₁-C₄ haloalkyl, or OH; piperidinyl, dihydropyridazinonyl, pyrrolidinonyl, thioxothiazolidinonyl, isoxazolyl, imidazolyl, or indolyl each of which is optionally substituted with 1, or 2 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, or C₂-C₄ alkanoyl; phenyl optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, OH, C₁-C₄ alkyl, C₁-C₄ alkoxy, or C₁-C₂ haloalkyl.

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-
[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-(3,3,3-
trifluoropropanoyl)-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-(trifluoroacetyl)-D-alaninamide;

N~2~-acetyl-3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-(pyridin-4-ylcarbonyl)-D-alaninamide;

3-(butylsulfonyl)-N~2~-(cyclopropylcarbonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-(beta-alanyl)-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-glycyl-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-(N,N-dimethylglycyl)-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-(N,N-dimethyl-beta-alanyl)-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-(methoxyacetyl)-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-(pyridin-3-ylcarbonyl)-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(2,4-dimethyl-1,3-thiazol-5-yl)carbonyl]-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-

[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-{[3-(trifluoromethyl)-1H-pyrazol-4-yl]carbonyl}-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(3-methyl-1H-pyrazol-5-yl)carbonyl]-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-(1H-imidazol-4-ylacetyl)-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-(pyrazin-2-ylcarbonyl)-D-alaninamide;

3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(6-hydroxypyridin-3-yl)carbonyl]-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-(cyclopropylamino)-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-N~2~-(pyridin-4-ylcarbonyl)-D-alaninamide;

N~2~-acetyl-3-(butylsulfonyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-methylbutyl)amino]-2-hydroxypropyl}-D-alaninamide;

N~1~-[(1S,2R)-3-(cyclopropylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-N~2~-(cyclopropylcarbonyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~2~-acetyl-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-methylbutyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-N~2~-(pyridin-4-ylcarbonyl)-D-alaninamide;

N~2~-[(5-bromoopyridin-3-yl)carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~2~-[(5-chloropyridin-3-yl)carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-(3-fluorobenzoyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-[(5-methylpyridin-3-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~2~-phenylglycyl-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-N~2~-{[3-(trifluoromethyl)-1H-pyrazol-4-yl]carbonyl}-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~-{[3-methyl-1H-pyrazol-5-yl]carbonyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-N~2~-{(1,3-thiazol-4-yl)carbonyl}-D-alaninamide;

N~2~-[(1-acetylpiperidin-4-yl)carbonyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~2~-[4-(acetylamino)butanoyl]-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~2~-acetyl-beta-alanyl-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~2~--(chloroacetyl)-N~1~-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-

propylbutyl)sulfonyl]-D-alaninamide;

N~1~--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~--(methoxyacetyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~1~--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~--(3-methoxypropanoyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~1~--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~--(2,2-dimethylpropanoyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~1~--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2~--isobutyryl-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~2~--butyryl-N~1~--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~2~--acetyl-N~1~--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~1~--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethylphenyl)cyclopropyl]amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-N~2~--[(pyridin-3-yl)carbonyl]-D-alaninamide trifluoroacetate;

N~1~--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethylphenyl)cyclopropyl]amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-N~2~--[(pyridin-4-yl)carbonyl]-D-alaninamide trifluoroacetate;

N~1~--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethylphenyl)cyclopropyl]amino]-2-hydroxypropyl}-N~2~--(3-hydroxybenzoyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide trifluoroacetate;

N~1~--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-N~2~--[(pyridin-3-yl)carbonyl]-D-

alaninamide;

N~1~-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N~2~-((3-hydroxybenzoyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~2~-((cyclopropylcarbonyl)-N~1~-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

N~1~-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N~2~-propionyl-3-[(1-propylbutyl)sulfonyl]-D-alaninamide;

3-[butylsulfonyl]-N~1~-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N~2~-[(pyridin-3-yl)carbonyl]-D,L-alaninamide;

N~1~-((1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethylphenyl)cyclopropyl]amino]-2-hydroxypropyl)-N~2~-((3-hydroxybenzoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide trifluoracetate;

N~1~-((1S,2R)-1-(3,5-difluorobenzyl)-3-[[1-(3-ethylphenyl)cyclopropyl]amino]-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]-N~2~-[(pyridin-4-yl)carbonyl]-D-alaninamide trifluoroacetate;

N~1~-((1S,2S)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N~2~-[(6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]alaninamide hydrochloride;

5-oxo-D-prolyl-N~1~-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]alaninamide;

5-oxo-L-prolyl-N~1~-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[(1-propylbutyl)sulfonyl]alaninamide;

N~1~-((1S,2S)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N~2~-[(3-(4-oxo-2-thioxo-1,3-thiazolidin-3-yl)propanoyl)-3-[(1-

propylbutyl)sulfonyl]alaninamide;

N~1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2--[(piperidin-4-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2--[(2,4-dimethyl-1,3-thiazol-5-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2--[(2-methyl-4-(trifluoromethyl)-1,3-thiazol-5-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2--[(3,5-dimethylisoxazol-4-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2--[(3-methyl-1H-pyrazol-5-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide trifluoroacetate;

N~1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2--[(1H-pyrazol-4-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2--[(1H-imidazol-5-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2--[(1H-imidazol-4-yl)acetyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-N~2--[(pyrazin-2-yl)carbonyl]-D,L-alaninamide;

N~1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-

ethylbenzyl) amino]-2-hydroxypropyl}-N-2--[(3,5-dihydroxypyridin-4-yl) carbonyl]--3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N-2--[(6-hydroxypyridin-3-yl) carbonyl]-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N-2--[(6-chloropyridin-3-yl) carbonyl]-N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl)-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-N-2--[(pyridin-4-yl) carbonyl]-D,L-alaninamide;

N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N-2--[(pyridin-3-yl) carbonyl]-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-N-2--[(pyridin-2-yl) carbonyl]-D,L-alaninamide;

N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N-2--[(1H-indole-6-carbonyl)-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-[(1-propylbutyl) sulfonyl]-N-2--(2,3,4-trimethoxybenzoyl)-D,L-alaninamide;

N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N-2--[(pyridin-2-yl) carbonyl]-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide;

N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N-2--(3-hydroxybenzoyl)-3-[(1-propylbutyl) sulfonyl]-D,L-alaninamide

N-1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-

ethylbenzyl)amino]-2-hydroxypropyl}-N~2--(3-methylbenzoyl)-3-
[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2--(3-ethylbenzoyl)-3-
[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~2--(3-chlorobenzoyl)-N~1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-
[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2--(4-methylbenzoyl)-3-
[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2--(4-methoxybenzoyl)-3-
[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2--(4-trifluoromethylbenzoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~2--(cyclohexylcarbonyl)-N~1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-
[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~2-(benzoyl)-N~1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~2-(benzoyl)-N~1--{(1S,2R)-3-(cyclopropylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]alaninamide;

N~1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2--(phenylacetyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N~1--{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N~2--(3-phenylpropanoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide;

N-(3-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-

ethylbenzyl)amino]-2-hydroxypropyl)amino)-3-oxo-2-[[(1-propylbutyl)sulfonyl)methyl]propyl)benzamide;

N~1~-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N~2~-{(cyclopropylacetyl)-3-[(1-propylbutyl)sulfonyl]}-D,L-alaninamide;

N~1~-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N~2~-[(methylsulfonyl)acetyl]-3-[(1-propylbutyl)sulfonyl]}-D,L-alaninamide;

N~1~-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N~2~-[(methylthio)acetyl]-3-[(1-propylbutyl)sulfonyl]}-D,L-alaninamide;

N~1~-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N~2~-{(4-hydroxy-4-oxobutanoyl)-3-[(1-propylbutyl)sulfonyl]}-D,L-alaninamide;

N~1~-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N~2~-[4-(methylamino)-4-oxobutanoyl]-3-[(1-propylbutyl)sulfonyl]}-D,L-alaninamide;

N~1~-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-N~2~-{(4-methoxy-4-oxobutanoyl)-3-[(1-propylbutyl)sulfonyl]}-D,L-alaninamide;

N-(methylsulfonyl)glycyl-N~1~-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-3-[(1-propylbutyl)sulfonyl]}-D,L-alaninamide;

N~2~-acetyl-N~1~-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-3-(phenylsulfonyl)}-D,L-alaninamide;

N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-(2S)-2-[(4-methoxy-4-oxobutanoyl)amino]-5-oxo-5-piperidin-1-ylpentanamide;

(2R)-2-[[(benzyloxy) carbonyl]amino]-N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-5-oxo-5-piperidin-1-ylpentanamide;

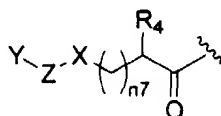
N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-(2R)-2-[(3-ethoxy-3-oxopropanoyl)amino]-5-oxo-5-piperidin-1-ylpentanamide;

N-1--((1S,2R)-1-benzyl-3-[(3-methoxybenzyl)amino]-2-hydroxypropyl)-N-2--(4-methoxy-4-oxobutanoyl)-N-5~,N-5--dipropyl-D-glutamamide;

N-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-(2R)-2-[(4-methoxy-4-oxobutanoyl)amino]-5-oxo-5-piperidin-1-ylpentanamide; and

N-((1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl)-(2R)-2-[(5-methoxy-5-oxopentanoyl)amino]-5-oxo-5-piperidin-1-ylpentanamide .

22. A compound according to claim 3, wherein R_N is of the formula:



5 wherein

n_7 is 0, 1, or 2;

R_4 is $-NHR_8$ or $-NH(CH_2)_{n_6}-R_{4-1}$; wherein

n_6 is 0, 1, 2, or 3;

10 R_{4-1} is selected from the group consisting of $-SO_2-(C_1-C_8$ alkyl), $-SO-(C_1-C_8$ alkyl), $-S-(C_1-C_8$ alkyl), $-S-CO-(C_1-C_6$ alkyl), $-SO_2-NR_{4-2}R_{4-3}$; $-CO-C_1-C_2$ alkyl; $-CO-NR_{4-3}R_{4-4}$;

R_{4-2} and R_{4-3} are independently H, C_1-C_3 alkyl, or C_3-C_6 cycloalkyl;

15 R_{4-4} is C_1-C_4 alkyl, phenyl C_1-C_4 alkyl, C_2-C_4 alkanoyl, or phenyl C_1-C_4 alkanoyl;

R_8 is selected from the group consisting of $-SO_2$ -heteroaryl optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl or halogen; $-SO_2$ -phenyl; $-SO_2$ -heterocycloalkyl; $-C(O)NHR_9$; heterocycloalkyl; $-S-C_2-C_4$ alkanoyl; wherein

20

R_9 is phenyl C_1-C_4 alkyl, C_1-C_6 alkyl, or H;

X is C₁-C₄ alkylidenyl optionally optionally substituted with
1, 2, or 3 methyl groups; or -NR₄₋₆-; or

R₄ and R₄₋₆ combine to form -(CH₂)_{n10}-, wherein

n₁₀ is 1, 2, 3, or 4;

5 Z is SO₂; SO; S; or C(O);

Y is H; C₁-C₄ haloalkyl; C₅-C₆ heterocycloalkyl containing at
least one N, O, or S; phenyl; OH; -N(Y₁)(Y₂); C₁-C₁₀ alkyl
optionally substituted with 1 thru 3 substituents which
can be the same or different and are selected from
10 halogen, hydroxy, alkoxy, thioalkoxy, and haloalkoxy; C₃-
C₈ cycloalkyl optionally substituted with 1, 2, or 3
groups independently selected from C₁-C₃ alkyl, and
halogen; alkoxy; phenyl optionally substituted with
halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, CN or NO₂; or phenyl C₁-
15 C₄ alkyl optionally substituted with halogen, C₁-C₄ alkyl,
C₁-C₄ alkoxy, CN or NO₂; wherein

Y₁ and Y₂ are the same or different and are H; C₁-C₁₀ alkyl
optionally substituted with 1, 2, or 3 substituents
selected from halogen, C₁-C₄ alkoxy, C₃-C₈ cycloalkyl,
20 and OH; C₂-C₆ alkenyl; C₂-C₆ alkanoyl; phenyl; -SO₂-C₁-
C₄ alkyl; phenyl C₁-C₄ alkyl; or C₃-C₈ cycloalkyl C₁-C₄
alkyl; or

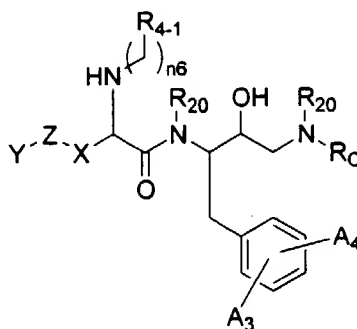
-N(Y₁)(Y₂) forms a ring selected from piperazinyl,
piperidinyl, morpholinyl, and pyrrolidinyl, wherein
25 each ring is optionally substituted with 1, 2, 3, or
4 groups that are independently C₁-C₆ alkyl, C₁-C₆
alkoxy, C₁-C₆ alkoxy C₁-C₆ alkyl, or halogen; and

R₂₀ at each occurrence is independently hydrogen, C₁-C₆ alkyl,
C₁-C₆ alkoxy C₁-C₆ alkyl, halo C₁-C₆ alkyl, or C₁-C₆
30 alkanoyl, each of which is unsubstituted or substituted
with 1, or 2 groups independently selected from halogen,
C₁-C₆ alkyl, hydroxy, C₁-C₆ alkoxy, NH₂, and -R₂₆-R₂₇,
wherein

R_{26} is $-C(O)-$, $-SO_2-$, $-CO_2-$, $-C(O)NH-$, or $-C(O)N(C_1-C_6 \text{ alkyl})-$;

R_{27} is C_1-C_6 alkyl, C_1-C_6 alkoxy, aryl C_1-C_6 alkyl, heterocycloalkyl, or heteroaryl, wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, halo C_1-C_6 alkyl, hydroxy C_1-C_6 alkyl, $-C(O)NH_2$, NH_2 , $NH(C_1-C_6 \text{ alkyl})$, $N(C_1-C_6 \text{ alkyl})(C_1-C_6 \text{ alkyl})$, $-C(O)NH(C_1-C_6 \text{ alkyl})$, or $-C(O)N(C_1-C_6 \text{ alkyl})(C_1-C_6 \text{ alkyl})$.

23. A compound according to claim 3, of the formula:



wherein

R_C is C_3-C_8 alkyl, cyclopropyl, cyclopentyl, cyclohexyl, or $-(C_1-C_4)\text{alkyl}-(C_3-C_6)\text{cycloalkyl}$.

24. A compound according to claim 1, wherein

R_4 is H; C_1-C_4 alkyl- $NHC(O)R_5$; $-(CH_2)_{0-4}R_8$; $-O-C_1-C_4$ alkanoyl; OH; C_6-C_{10} aryloxy optionally substituted with 1, 2, or 3 groups that are independently halogen, C_1-C_4 alkyl, CO_2H , $-C(O)-C_1-C_4$ alkoxy, or C_1-C_4 alkoxy; C_1-C_6 alkoxy; aryl C_1-C_4 alkoxy; $-C_1-C_4$ alkyl- $NR_{50}CO_2R_{51}$; $-C\equiv N$; $-CF_3$; $-CF_2-CF_3$; $-C\equiv CH$; $-CH_2-CH=CH_2$; $-(CH_2)_{1-4}-R_{4-1}$; $-(CH_2)_{1-4}-NH-R_{4-1}$; $-O-(CH_2)_{n6}-R_{4-1}$; $S-(CH_2)_{n6}-R_{4-1}$; $(CH_2)_{0-4}-NHC(O)-(CH_2)_{0-6}-R_{52}$; or $-(CH_2)_{0-4}-R_{53}-(CH_2)_{0-4}-R_{54}$.

25. A compound according to claim 24, wherein

R_1 is $(CH_2)_{n1}-(R_{1-aryl})$ where n_1 is zero or one and R_{1-aryl} is phenyl optionally substituted with 1, 2, 3, or 4 groups independently selected from C_1-C_6 alkyl optionally substituted with 1, 2, or 3 substituents selected from the group consisting of C_1-C_3 alkyl, halogen, $-OH$, $-SH$,
5 $-NR_{1-a}R_{1-b}$, $-C\equiv N$, $-CF_3$, and C_1-C_3 alkoxy; halogen; C_1-C_6 alkoxy; $-NR_{N-2}R_{N-3}$; and OH ; wherein

R_{N-2} and R_{N-3} at each occurrence are independently selected from the group consisting of $-C_1-C_8$ alkyl optionally substituted with 1, 2, or 3 groups independently
10 selected from the group consisting of $-OH$, $-NH_2$, phenyl and halogen; $-C_3-C_8$ cycloalkyl; $-(C_1-C_2 \text{ alkyl})-(C_3-C_8 \text{ cycloalkyl})$; $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_3 \text{ alkyl})$; $-C_2-C_6$ alkenyl; $-C_2-C_6$ alkynyl; $-C_1-C_6$ alkyl chain with
15 one double bond and one triple bond; aryl; heteroaryl; heterocycloalkyl;

or

R_{N-2} , R_{N-3} and the nitrogen to which they are attached form a 5, 6, or 7 membered heterocycloalkyl or heteroaryl group, wherein said heterocycloalkyl or heteroaryl
20 group is optionally fused to a benzene, pyridine, or pyrimidine ring, and said groups are unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that at each occurrence are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, halo C_1-C_6 alkyl, halo C_1-C_6 alkoxy,
25 $-CN$, $-NO_2$, $-NH_2$, $NH(C_1-C_6 \text{ alkyl})$, $N(C_1-C_6 \text{ alkyl})(C_1-C_6 \text{ alkyl})$, $-OH$, $-C(O)NH_2$, $-C(O)NH(C_1-C_6 \text{ alkyl})$, $-C(O)N(C_1-C_6 \text{ alkyl})(C_1-C_6 \text{ alkyl})$, C_1-C_6 alkoxy C_1-C_6 alkyl, C_1-C_6 thioalkoxy, and C_1-C_6 thioalkoxy C_1-C_6
30 alkyl.

26. A compound according to claim 25, wherein
 R_{20} at each occurrence is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_4 alkoxy C_1-C_4 alkyl, halo C_1-C_6 alkyl, C_2-

C₄ alkanoyl, each of which is unsubstituted or substituted with 1, or 2 groups independently selected from halogen, C₁-C₆ alkyl, hydroxy, C₁-C₆ alkoxy, NH₂, and -R₂₆-R₂₇, wherein

5 R₂₆ is selected from -C(O)-, -SO₂-, -CO₂-;

R₂₇ is selected from C₁-C₆ alkyl, C₁-C₆ alkoxy, aryl C₁-C₆ alkyl, piperidyl, pyrrolyl, and pyridyl, wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, halo C₁-C₆ alkyl, hydroxy C₁-C₆ alkyl, -C(O)NH₂, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)(C₁-C₆ alkyl), -C(O)NH(C₁-C₆ alkyl), or -C(O)N(C₁-C₆ alkyl)(C₁-C₆ alkyl).

15 27. A compound according to claim 26, wherein

R₄ is H; C₁-C₄ alkyl-NHC(O)R₅; -(CH₂)₀₋₄R₈; -C₁-C₄ alkyl-NR₅₀CO₂R₅₁; -C≡N; -CF₃; -CF₂-CF₃; -C≡CH; -CH₂-CH=CH₂; -(CH₂)₁₋₄-R₄₋₁; -(CH₂)₁₋₄-NH-R₄₋₁; (CH₂)₀₋₄-NHC(O)-(CH₂)₀₋₆-R₅₂; or -(CH₂)₀₋₄-R₅₃-(CH₂)₀₋₄-R₅₄.

20

28. A compound according to claim 27, wherein

X is C₁-C₄ alkylidenyl optionally optionally substituted with 1, 2, or 3 methyl groups; or -NR₄₋₆-; or

R₄ and R₄₋₆ combine to form -(CH₂)_{n10}-, wherein

25 n₁₀ is 1, 2, 3, or 4;

Z is selected from a bond; SO₂; SO; S; and C(O);

Y is selected from H; C₁-C₄ haloalkyl; C₅-C₆ heterocycloalkyl containing at least one N, O, or S; phenyl; OH; -

30 N(Y₁)(Y₂); C₁-C₁₀ alkyl optionally substituted with 1 thru 3 substituents which can be the same or different and are selected from halogen, hydroxy, alkoxy, thioalkoxy, and haloalkoxy; C₃-C₈ cycloalkyl optionally substituted with 1, 2, or 3 groups independently selected from C₁-C₃ alkyl, and halogen; alkoxy; phenyl optionally substituted with

halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, CN or NO₂; phenyl C₁-C₄ alkyl optionally substituted with halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, CN or NO₂; wherein

Y₁ and Y₂ are the same or different and are H; C₁-C₁₀ alkyl

5 optionally substituted with 1, 2, or 3 substituents selected from the group consisting of halogen, C₁-C₄ alkoxy, C₃-C₈ cycloalkyl, and OH; C₂-C₆ alkenyl; C₂-C₆ alkanoyl; phenyl; -SO₂-C₁-C₄ alkyl; phenyl C₁-C₄ alkyl; and C₃-C₈ cycloalkyl C₁-C₄ alkyl; or

10 -N(Y₁)(Y₂) forms a ring selected from piperazinyl, piperidinyl, morpholinyl, and pyrrolidinyl, wherein each ring is optionally substituted with 1, 2, 3, or 4 groups that are independently C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkoxy C₁-C₆ alkyl, or halogen.

15

29. A compound according to claim 28, wherein

R₂₀ at each occurrence is independently selected from hydrogen, C₁-C₆ alkyl, C₁-C₄ alkoxy C₁-C₄ alkyl, C₂-C₄ alkanoyl, tertiary-butoxy carbonyl, and benzyloxycarbonyl;

20 R₁ is benzyl which is optionally substituted with 1, 2, 3, or 4 groups independently selected from halogen, C₁-C₄ alkoxy, hydroxy, and C₁-C₄ alkyl optionally substituted with 1, 2, or 3 substituents halogen, OH, SH, NH₂, NH(C₁-C₆ alkyl), N-(C₁-C₆ alkyl)(C₁-C₆ alkyl), C≡N, CF₃;

25 R₂ and R₃ are independently selected from H or C₁-C₄ alkyl optionally substituted with 1 substituent selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, NH₂, NH(C₁-C₆ alkyl), and NH(C₁-C₆ alkyl)(C₁-C₆ alkyl);

R₂₀ at each occurrence is independently hydrogen, C₁-C₆ alkyl, 30 C₁-C₂ alkoxy C₁-C₄ alkyl, halo C₁-C₄ alkyl, C₂-C₆ alkanoyl, each of which is unsubstituted or substituted with 1 or 2 groups independently selected from halogen, hydroxy, and NH₂;

R_C is C₁-C₈ alkyl optionally substituted with 1, 2, or 3 groups independently selected from R₂₀₅, -SH, -C=ONR₂₃₅R₂₄₀, and -S(=O)₂NR₂₃₅R₂₄₀; -(CH₂)₀₋₃-(C₃-C₆) cycloalkyl wherein the cycloalkyl is optionally substituted with 1, 2, or 3

5 groups independently selected from R₂₀₅, -CO₂H, and -CO₂-(C₁-C₄ alkyl); -(CR₂₄₅R₂₅₀)₀₋₄-phenyl optionally substituted with 1, 2, or 3 R₂₀₀; -(CR₂₄₅R₂₅₀)₀₋₃-pyridyl; -(CR₂₄₅R₂₅₀)₀₋₃-pyridazinyl; -(CR₂₄₅R₂₅₀)₀₋₃-pyrimidinyl; -(CR₂₄₅R₂₅₀)₀₋₃-pyrazinyl; -(CR₂₄₅R₂₅₀)₀₋₃-furyl; -(CR₂₄₅R₂₅₀)₀₋₃-indolyl; 10 -(CR₂₄₅R₂₅₀)₀₋₃-thienyl; -(CR₂₄₅R₂₅₀)₀₋₃-pyrrolyl; -(CR₂₄₅R₂₅₀)₀₋₃-pyrazolyl; (CR₂₄₅R₂₅₀)₀₋₃-benzoxazolyl; -(CR₂₄₅R₂₅₀)₀₋₃-imidazolyl; each of the above heteroaryl groups is optionally substituted with 1, 2, 3, or 4 R₂₀₀; -(CR₂₄₅R₂₅₀)₀₋₃-imidazolidinyl; (CR₂₄₅R₂₅₀)₀₋₃-tetrahydrofuryl; (CR₂₄₅R₂₅₀)₀₋₃-tetrahydropyranyl; (CR₂₄₅R₂₅₀)₀₋₃-piperazinyl; (CR₂₄₅R₂₅₀)₀₋₃-pyrrolidinyl; (CR₂₄₅R₂₅₀)₀₋₃-piperidinyl; (CR₂₄₅R₂₅₀)₀₋₃-indolinyl; each of the above heterocycloalkyl groups is optionally substituted with 1, 2, 3, or 4 R₂₁₀; (CH₂)₀₋₁-CH((CH₂)₀₋₄-OH)-(CH₂)₀₋₁-phenyl; -(CH₂)₀₋₁-CH(C₁-C₄ hydroxyalkyl)-(CH₂)₀₋₁-pyridyl;

20 R₂₀₀ at each occurrence is independently C₁-C₆ alkyl optionally substituted with 1, 2, or 3 R₂₀₅ groups; OH; -NO₂; halogen; -CO₂H; C≡N; -(CH₂)₀₋₄-CO-NR₂₂₀R₂₂₅; -(CH₂)₀₋₄-CO-(C₁-C₈ alkyl); -(CH₂)₀₋₄-CO₂R₂₁₅; and - 25 (CH₂)₀₋₄-O-(C₁-C₆ alkyl optionally substituted with 1, 2, 3, or 5 -F);

R₂₀₅ at each occurrence is independently C₁-C₆ alkyl, halogen, -OH, -O-phenyl, -SH, -C≡N, -CF₃, C₁-C₆ alkoxy, NH₂, NH(C₁-C₆ alkyl), and N-(C₁-C₆ alkyl)(C₁-C₆ alkyl); 30

R₂₁₀ at each occurrence is independently C₁-C₆ alkyl optionally substituted with 1 or 2 R₂₀₅ groups; halogen; C₁-C₄ alkoxy; C₁-C₄ haloalkoxy; -NR₂₂₀R₂₂₅; OH; C≡N; C₃-C₇ cycloalkyl optionally substituted with 1

or 2 R_{205} groups; $-\text{CO}-(\text{C}_1-\text{C}_4 \text{ alkyl})$; $-\text{SO}_2-\text{NR}_{235}\text{R}_{240}$; $-\text{CO}-\text{NR}_{235}\text{R}_{240}$; $-\text{SO}_2-(\text{C}_1-\text{C}_4 \text{ alkyl})$; and $=\text{O}$; wherein

R_{215} at each occurrence is independently C_1-C_6 alkyl, $-(\text{CH}_2)_{0-2}-(\text{phenyl})$, C_3-C_6 cycloalkyl, $-(\text{CH}_2)_{0-2}-(\text{pyridyl})$, $-(\text{CH}_2)_{0-2}-(\text{pyrrolyl})$, $-(\text{CH}_2)_{0-2}-(\text{imidazolyl})$, $-(\text{CH}_2)_{0-2}-(\text{pyrimidyl})$, $-(\text{CH}_2)_{0-2}-(\text{pyrrolidinyl})$, $-(\text{CH}_2)_{0-2}-(\text{imidazolidinyl})$, $-(\text{CH}_2)_{0-2}-(\text{piperazinyl})$, $-(\text{CH}_2)_{0-2}-(\text{piperidinyl})$, and $-(\text{CH}_2)_{0-2}-(\text{morpholinyl})$; wherein the phenyl group at each occurrence is optionally substituted with 1 or 2 groups that are independently R_{205} or R_{210} ; wherein each heterocycloalkyl group at each occurrence is optionally substituted with 1 or 2 R_{210} ; wherein each heteroaryl group at each occurrence is optionally substituted with 1 or 2 R_{210} ;

R_{220} and R_{225} at each occurrence are independently $-\text{H}$, $-\text{C}_1-\text{C}_4$ alkyl, hydroxy C_1-C_4 alkyl, halo C_1-C_4 alkyl; $-\text{C}_3-\text{C}_6$ cycloalkyl, and $-(\text{C}_1-\text{C}_4 \text{ alkyl})-\text{O}-(\text{C}_1-\text{C}_2 \text{ alkyl})$;

R_{235} and R_{240} at each occurrence are independently H , or C_1-C_6 alkyl;

R_{245} and R_{250} at each occurrence are independently H , C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, or

R_{245} and R_{250} are taken together with the carbon to which they are attached to form a carbocycle of 3, 5, or 6 carbon atoms.

30. A compound according to claim 29 wherein

R_4 is H ; C_1-C_4 alkyl- $\text{NHC}(\text{O})\text{R}_5$; $-(\text{CH}_2)_{0-4}\text{R}_8$; $-\text{C}_1-\text{C}_4$ alkyl- $\text{NR}_{50}\text{CO}_2\text{R}_{51}$; $-(\text{CH}_2)_{1-4}-\text{R}_{4-1}$; $-(\text{CH}_2)_{1-4}-\text{NH}-\text{R}_{4-2}$; $(\text{CH}_2)_{1-4}-\text{NHC}(\text{O})-(\text{CH}_2)_{0-6}-\text{R}_{52}$; or $-(\text{CH}_2)_{1-4}-\text{R}_{53}-(\text{CH}_2)_{0-4}-\text{R}_{54}$; wherein

R_{4-1} is $-\text{SO}_2-(\text{C}_1-\text{C}_8 \text{ alkyl})$, $-\text{SO}_2-\text{NR}_{4-2}\text{R}_{4-3}$; or $-\text{CO}-\text{NR}_{4-3}\text{R}_{4-4}$;

wherein

R_{4-2} and R_{4-3} are independently H , or C_1-C_3 alkyl;

R₄₋₄ is C₁-C₄ alkyl, phenyl C₁-C₄ alkyl, C₂-C₄ alkanoyl, or phenyl C₁-C₄ alkanoyl;

R₅ is selected from the group consisting of cyclopropyl;

cyclopentyl; cyclohexyl; C₁-C₆ alkyl optionally

5 substituted with 1, 2, or 3 groups that are

independently halogen, -NR₆R₇, C₁-C₄ alkoxy, C₅-C₆

heterocycloalkyl, C₅-C₆ heteroaryl, phenyl, C₃-C₇

cycloalkyl, -S-C₁-C₄ alkyl, -SO₂-C₁-C₄ alkyl, -CO₂H,

-CONR₆R₇, -CO₂-C₁-C₄ alkyl, or phenyloxy; pyridyl,

10 thiazolyl, pyrazolyl, pyrazinyl, optionally

substituted with 1, 2, or 3 groups that are

independently C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, C₁-C₄

haloalkyl, or OH; piperidinyl, dihydropyridazinonyl,

pyrrolidinonyl, thioxothiazolidinonyl, isoxazolyl,

15 imidazolyl, indolyl, optionally substituted with 1,

2, or 3 groups that are independently C₁-C₄ alkyl, C₁-

C₄ alkoxy, halogen, or C₂-C₄ alkanoyl; phenyl

optionally substituted with 1, 2, 3, or 4 groups that

are independently halogen, OH, C₁-C₄ alkyl, C₁-C₄

20 alkoxy, or C₁-C₄ haloalkyl; wherein

R₆ and R₇ are independently selected from the group

consisting of H, C₁-C₆ alkyl, C₂-C₆ alkanoyl, phenyl,

-SO₂-C₁-C₄ alkyl, benzyl, and phenethyl;

R₈ is -SO₂-thienyl optionally substituted with 1 or 2

25 groups that are independently C₁-C₄ alkyl or halogen;

-SO₂-phenyl, -SO₂-piperidinyl, -SO₂-pyrrolidinyl,

imidazolidinyyl dione, -C(O)NHR₉, -S-C₁-C₆ alkyl, or -

S-C₂-C₄ alkanoyl, wherein

R₉ is phenyl C₁-C₄ alkyl, C₁-C₄ alkyl, or H;

30 R₅₀ is H or C₁-C₄ alkyl;

R₅₁ is selected from benzyl; phenethyl; C₁-C₆ alkyl

optionally substituted with 1, 2, or 3 groups that

are independently halogen, cyano, -NR₆R₇, -C(O)NR₆R₇,

or -C₁-C₄ alkoxy; heterocycloalkyl containing at

least one N, O, or S and optionally substituted with
1 or 2 groups that are independently C₁-C₄ alkyl, C₁-
C₄ alkoxy, halogen, C₂-C₄ alkanoyl, phenyl C₁-C₄
alkyl, and -SO₂ C₁-C₄ alkyl; heterocycloalkylalkyl
5 containing at least one N, O, or S and optionally
substituted with 1 or 2 groups that are independently
C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, C₂-C₄ alkanoyl,
phenyl C₁-C₄ alkyl, and -SO₂ C₁-C₄ alkyl; C₂-C₆
alkenyl; C₂-C₆ alkynyl; heteroaryl optionally
10 substituted with 1, 2, or 3 groups that are
independently OH, C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen,
NH₂, NH(C₁-C₆ alkyl) or N(C₁-C₆ alkyl)(C₁-C₆ alkyl);
heteroarylalkyl containing at least one N, O, or S
and optionally substituted with 1, 2, or 3 groups
15 that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy,
halogen, NH₂, NH(C₁-C₆ alkyl) or N(C₁-C₆ alkyl)(C₁-C₆
alkyl); phenyl; C₃-C₆ cycloalkyl, and C₃-C₆ cycloalkyl
C₁-C₄ alkyl, wherein the phenyl; C₃-C₆ cycloalkyl, and
C₃-C₆ cycloalkyl C₁-C₄ alkyl groups are optionally
20 substituted with 1, 2, or 3 groups that are
independently halogen, CN, NO₂, C₁-C₄ alkyl, C₁-C₄
alkoxy, C₂-C₆ alkanoyl, C₁-C₄ haloalkyl, C₁-C₄
haloalkoxy, hydroxy, C₁-C₄ hydroxyalkyl, C₁-C₄
thioalkoxy;

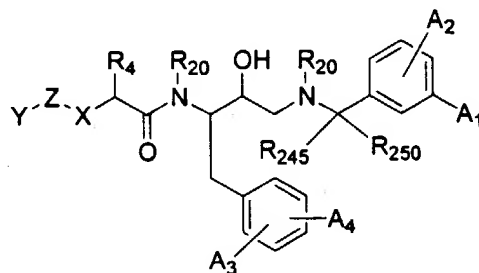
25 R₅₂ is heterocycloalkyl, heteroaryl, phenyl, C₃-C₆
cycloalkyl, -S(O)₀₋₂-C₁-C₆ alkyl, CO₂H, -C(O)NH₂,
-C(O)NH(alkyl), -C(O)N(alkyl)(alkyl), -CO₂-alkyl,
-NHS(O)₀₋₂-C₁-C₆ alkyl, -N(alkyl)S(O)₀₋₂-C₁-C₆ alkyl,
-S(O)₀₋₂-heteroaryl, -S(O)₀₋₂-aryl, -NH(arylalkyl),
30 -N(alkyl)(arylalkyl), thioalkoxy, or alkoxy, each of
which is optionally substituted with 1, 2, 3, 4, or 5
groups that are independently C₁-C₄ alkyl, C₁-C₄
alkoxy, C₁-C₄ thioalkoxy, halogen, C₁-C₄ haloalkyl,

haloalkoxy, C₂-C₆ alkanoyl, NO₂, CN, C₁-C₄
 alkoxy, carbonyl, or aminocarbonyl;

R₅₃ is absent, -O-, -C(O)-, -NH-, -N(alkyl)-, -NH-S(O)₀₋₂-,
 -N(alkyl)-S(O)₀₋₂-, -S(O)₀₋₂-NH-, or -S(O)₀₋₂-N(alkyl)-;

5 R₅₄ is pyridyl, thienyl, imidazolyl, phenyl, phenyl C₁-C₄
 alkyl, piperidyl, pyrrolidinyl, imidazolidinyl dione,
 CO₂H, -CO₂-alkyl, -C(O)NH(alkyl), -C(O)N(alkyl)
 (alkyl), -C(O)NH₂, C₁-C₈ alkyl, OH, phenoxy, alkoxy,
 phenylalkoxy, NH₂, NH(alkyl), N(alkyl) (alkyl), or -
 10 C₁-C₆ alkyl-CO₂-C₁-C₆ alkyl, each of which is
 optionally substituted with 1, 2, 3, 4, or 5 groups
 that are independently alkyl, alkoxy, CO₂H, -CO₂-
 alkyl, thioalkoxy, halogen, haloalkyl, haloalkoxy,
 hydroxyalkyl, alkanoyl, NO₂, CN, alkoxy, carbonyl, or
 15 aminocarbonyl.

31. A compound according to claim 30 of the formula:



20 wherein

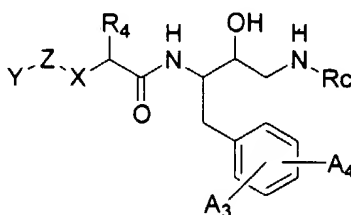
A₁ is H, C₁-C₄ alkyl or C₁-C₄ alkoxy;

A₂ is H, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, C₁-C₄
 haloalkyl or OH;

A₃ and A₄ are independently C₁-C₄ alkyl, halogen, or H.

25

32. A compound according to claim 30 of the formula:



wherein

R_C is C₃-C₈ alkyl, cyclopropyl, cyclopentyl, cyclohexyl, or -
(C₁-C₄)alkyl-(C₃-C₆) cycloalkyl; and

5 A₃ and A₄ are independently C₁-C₄ alkyl, halogen, or H.

33. A compound according to claim 1, wherein

R₄ is -C₁-C₄ alkyl-NR₅₀CO₂R₅₁; -(CH₂)₁₋₄-NH-R₄₋₁; or (CH₂)₁₋₄-NHC(O)-
(CH₂)₀₋₆-R₅₂; wherein

10 R₅₀ is H or C₁-C₄ alkyl;

R₅₁ is selected from benzyl; phenethyl; C₁-C₆ alkyl

optionally substituted with 1, 2, or 3 groups that
are independently halogen, cyano, -NR₆R₇, -C(O)NR₆R₇,
or -C₁-C₄ alkoxy; heterocycloalkyl containing at

15 least one N, O, or S and optionally substituted with
1 or 2 groups that are independently C₁-C₄ alkyl, C₁-
C₄ alkoxy, halogen, C₂-C₄ alkanoyl, phenyl C₁-C₄
alkyl, and -SO₂ C₁-C₄ alkyl; heterocycloalkylalkyl

containing at least one N, O, or S and optionally
20 substituted with 1 or 2 groups that are independently
C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, C₂-C₄ alkanoyl,
phenyl C₁-C₄ alkyl, and -SO₂ C₁-C₄ alkyl; C₂-C₆
alkenyl; C₂-C₆ alkynyl; heteroaryl optionally

substituted with 1, 2, or 3 groups that are
25 independently OH, C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen,
NH₂, NH(C₁-C₆ alkyl) or N(C₁-C₆ alkyl)(C₁-C₆ alkyl);

heteroarylalkyl containing at least one N, O, or S
and optionally substituted with 1, 2, or 3 groups
that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy,

30 halogen, NH₂, NH(C₁-C₆ alkyl) or N(C₁-C₆ alkyl)(C₁-C₆
alkyl); phenyl; C₃-C₆ cycloalkyl, and C₃-C₆ cycloalkyl

C₁-C₄ alkyl, wherein the phenyl; C₃-C₆ cycloalkyl, and C₃-C₆ cycloalkyl C₁-C₄ alkyl groups are optionally substituted with 1, 2, or 3 groups that are independently halogen, CN, NO₂, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₂-C₆ alkanoyl, C₁-C₄ haloalkyl, C₁-C₄ haloalkoxy, hydroxy, C₁-C₄ hydroxyalkyl, C₁-C₄ thioalkoxy;

R₆ and R₇ are independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkanoyl, phenyl, -SO₂-C₁-C₄ alkyl, benzyl, and phenethyl;

R₅₂ is heterocycloalkyl, heteroaryl, phenyl, C₃-C₆ cycloalkyl, -S(O)₀₋₂-C₁-C₆ alkyl, CO₂H, -C(O)NH₂, -C(O)NH(alkyl), -C(O)N(alkyl)(alkyl), -CO₂-alkyl, -NHS(O)₀₋₂-C₁-C₆ alkyl, -N(alkyl)S(O)₀₋₂-C₁-C₆ alkyl, -S(O)₀₋₂-heteroaryl, -S(O)₀₋₂-aryl, -NH(arylalkyl), -N(alkyl)(arylalkyl), thioalkoxy, or alkoxy, each of which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ thioalkoxy, halogen, C₁-C₄ haloalkyl, haloalkoxy, C₂-C₆ alkanoyl, NO₂, CN, C₁-C₄ alkoxycarbonyl, or aminocarbonyl.

34. A compound according to claim 33, wherein

R₄ is -O-C₁-C₄ alkanoyl; OH; phenyloxy or naphthyloxy, each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, C₁-C₄ alkyl, CO₂H, -C(O)-C₁-C₄ alkoxy, or C₁-C₄ alkoxy; C₁-C₆ alkoxy; phenyl C₁-C₄ alkoxy; -O-(CH₂)_{n6}-R₄₋₁; or -S-(CH₂)_{n6}-R₄₋₁

R₄₋₁ is -SO₂-(C₁-C₃ alkyl), -SO₂-NR₄₋₂R₄₋₃; or -CO-NR₄₋₃R₄₋₄; wherein

R₄₋₂ and R₄₋₃ are independently H, or C₁-C₃ alkyl;

R₄₋₄ is C₁-C₄ alkyl, phenyl C₁-C₄ alkyl, C₂-C₄ alkanoyl, or phenyl C₁-C₄ alkanoyl;

35. A method for the treatment or prevention of Alzheimer's disease, mild cognitive impairment Down's syndrome, Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, cerebral amyloid angiopathy, other degenerative
5 dementias, dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, diffuse Lewy body type of Alzheimer's disease comprising administration of a
10 therapeutically effective amount of a compound or salt according to Claim 1, to a patient in need thereof.

36. A method of treatment as in claim 35, wherein the patient is a human.

15

37. A method of treatment according to claim 35, wherein the disease is dementia.

20